

# **Study of Chiral Iridium N,P Ligand Complexes as Catalysts for the Asymmetric Hydrogenation of Different Substrate Classes**

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*“Asymmetric Hydrogenation of  $\alpha,\beta$ -Unsaturated Carboxylic Esters with Chiral Iridium N,P Ligand Complexes”*

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# Chapter 1

## Introduction

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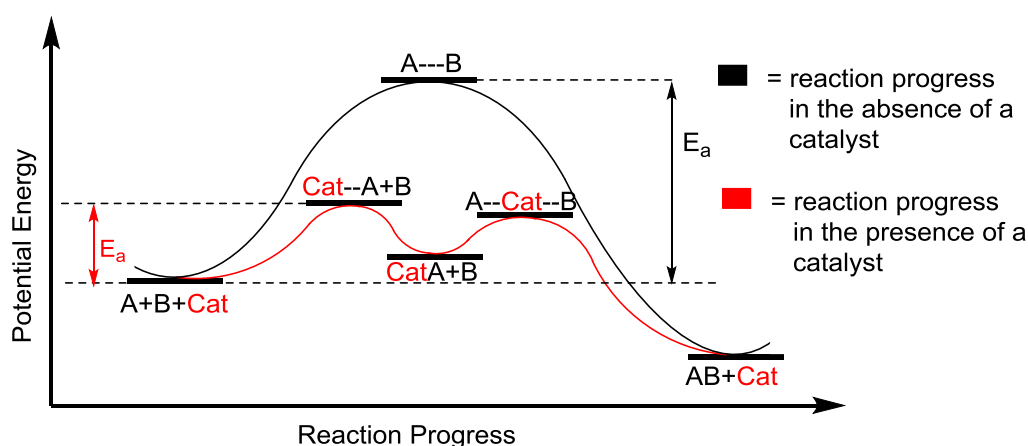
## 1.1 Asymmetric catalysis

### 1.1.1. Catalysis

*“A catalyst accelerates a chemical reaction without affecting the position of the equilibrium.”*

This still valid definition of a catalyst was coined by Wilhelm Ostwald, who already in 1895 realized catalysis as an ubiquitous phenomenon.<sup>[1]</sup>

Catalysts have always had a significant impact on the industrial development and it is estimated that ~90% of all chemically obtained industrial goods came in contact with catalysts at least once during their production.<sup>[2]</sup> By altering the activation energy of a given reaction, catalysts change the kinetic parameters of chemical processes (figure 1.1). Therefore, catalysts can accelerate or initiate a chemical reaction which will otherwise require long reaction times or will never occur in the absence of a catalyst. Hence, catalysis has a significant impact on our society. Based on the development of suitable catalysts, many important industrial processes were introduced, for example, the Haber-Bosch process used for the synthesis of ammonia from its elements, serving as a starting point for important components of fertilizers, medicaments, dyes, explosives or resins.<sup>[3]</sup>

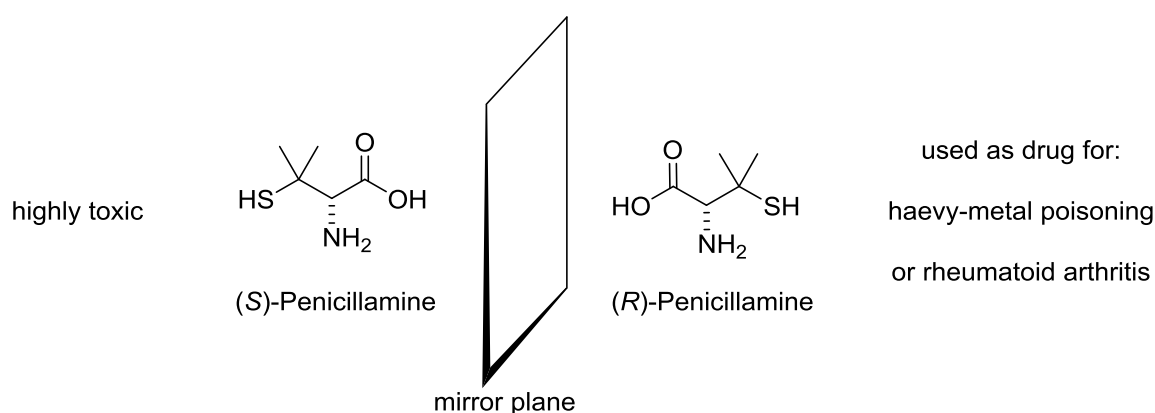


**Figure 1.1:** Simplified depiction of the mode of action of a catalyst.

### 1.1.2 Enantioselectivity

Another important research area affecting many different neighboring fields deals with the selective introduction of chirality into molecules.<sup>[4]</sup> Chirality is defined as: “the geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable on its mirror image; such an object has no symmetry elements of the second

kind (a mirror plane,  $\sigma = S_1$ , a centre of inversion,  $i = S_2$ , a rotation-reflection axis,  $S_{2n}$ ). One of a pair of molecular entities which are mirror images of each other and non-superposable,” are termed enantiomers.<sup>[5]</sup> The most frequent origin of chirality is based on a carbon atom bearing four different substituents. In an achiral environment the enantiomers have the same physical properties. However, when they are exposed to a chiral environment, such as biological systems, a significantly different behavior of two enantiomers can be observed. For example, they can smell or taste differently or they can have a contrary biological effect, like in the case of penicillamine where the (*R*)-enantiomer is highly toxic but the (*S*)-enantiomer is used for the treatment of heavy-metal poisoning or rheumatoid arthritis (figure 1.2).<sup>[6]</sup>



**Figure 1.2:** Penicillamine: the pair of enantiomers and their different effects in the human body.

Therefore, most of the chiral active pharmaceutical ingredients that are introduced on the market nowadays are pure enantiomers.<sup>[7]</sup> To allow for the production of enantiomerically pure substances different approaches exist.

One possibility is to start from molecules which are available from the chiral pool, using these substances to generate chiral molecules of higher complexity. Common chiral starting materials include amino acids, monosaccharides or hydroxy acids.<sup>[8]</sup> Therefore, the molecular diversity which can be easily accessed is restricted and furthermore, in the majority of the cases, only one enantiomer is available while the other enantiomer is extremely expensive.

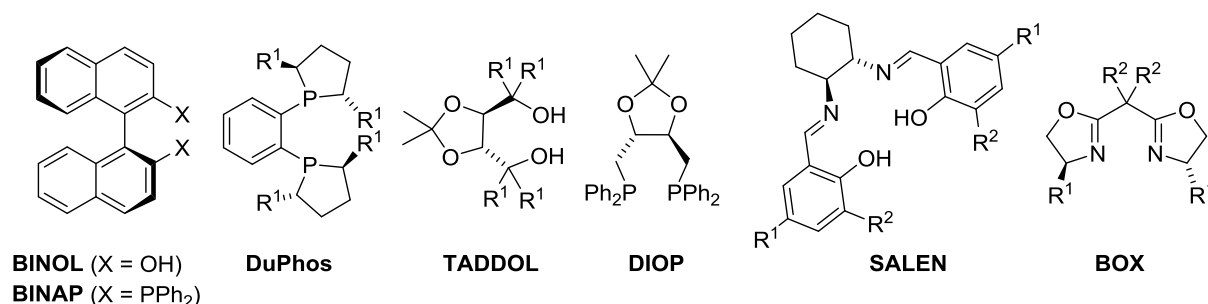
An alternative approach is the application of chiral auxiliaries, which are covalently bound to the substrate. This strategy allows for a substrate-controlled diastereoselective synthesis. However, the use of usually expensive, stoichiometric amounts of auxiliaries and the necessity to split off this part of the molecule in the end of the synthesis are a clear drawback.<sup>[9]</sup>

Among all possible methods to obtain the desired enantiomerically pure compounds, asymmetric catalysis represent the best option in many cases.<sup>[10]</sup> The successive development of different chiral catalysts over the last years allowed for the application of many different synthetic transformations with high enantioselectivity and efficiency.

## 1.2 Asymmetric hydrogenation

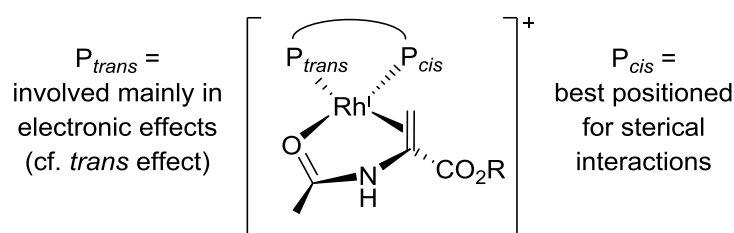
Among many different catalysts that have been developed for asymmetric transformations so far, transition metal-based complexes containing a chiral ligand transferring its chiral information in the course of the reaction to the substrate are the most common ones. In this context, transition metal-catalyzed asymmetric hydrogenation is one of the most established transformations. Furthermore, based on important attributes such as perfect atom economy, mild reaction conditions, low catalyst loadings, high conversions and high enantioselectivities which have been achieved for many asymmetric hydrogenations, this reaction is one of the most commonly applied in industry and academia.<sup>[11]</sup> In particular complexes based on ruthenium or rhodium have emerged as efficient catalysts and have found broad application in many industrial processes. The impact of these catalysts was recognized by awarding Ryoji Noyori and William S. Knowles the Nobel Prize in 2001 for their work “on chirally catalyzed hydrogenation reactions” .<sup>[12]</sup>

The progress of asymmetric hydrogenation is driven largely by the invention of new ligands and a larger number of chiral phosphine ligands are known which induce high enantioselectivity in rhodium- and ruthenium-catalyzed hydrogenations. A concept often recurring in the development of more efficient catalysts was the introduction of  $C_2$ -symmetric bidentate ligands. For such ligands the number of undesired, competing diastereoselective transition states, lowering the selectivity of the reactions, can be reduced compared to  $C_1$ -symmetric bidentate ligands. Furthermore, the relatively easy access to  $C_2$ -symmetric ligands by employing dimerization strategies of chiral monomeric units, the reduced complexity of NMR analysis for mechanistic investigations and the rationalization for the enantioselective outcome of reactions, were strong arguments in favor of this concept.<sup>[13]</sup> A survey of chiral ligands reveals that many broadly applied ligands possess  $C_2$  symmetry (figure 1.3).



**Figure 1.3:** Selection of ligands possessing  $C_2$  symmetry.

However, in the early 1990s, Achiwa and co-workers conducted a study aiming at the improvement of well-established P,P-ligands for the Rh-catalyzed hydrogenation of C=C bonds with adjacent coordinating groups.<sup>[14]</sup> The mechanism of the hydrogenation of dehydroamino acid derivatives had already been elucidated at this time. On the basis of the catalytic cycle they postulated the “Respective Control Concept” recognizing that in the crucial steps of the reaction, the two phosphines exhibit a different spatial orientation. Hence, these two phosphines play different roles in the catalytic cycle. The phosphine in *cis*-orientation to the C=C bond reveals significantly more steric interaction with the olefin and therefore is primarily responsible for the enantiomeric outcome of the reaction. The phosphine in *trans*-position to the C=C bond is better suited for electronic interaction with the substrate and hence mainly affects the reaction rate (figure 1.4).



**Figure 1.4:** Intermediate in the Rh-catalyzed asymmetric hydrogenation used to explain the “Respective Control Concept” by Achiwa and co-workers.

Based on this concept, Achiwa and co-workers successfully demonstrated that by the right choice of the phosphine unit the results in the hydrogenation of dimethyl itaconate (**1.1**) can be improved (table 1.1). Using a non- $C_2$ -symmetric BPPM derived ligand (**1.3**) both reactivity and selectivity of the reaction significantly increased to the optimal combination (entry 3).

**Table 1.1:** Asymmetric hydrogenation of dimethyl itaconate using ligand with different phosphines.

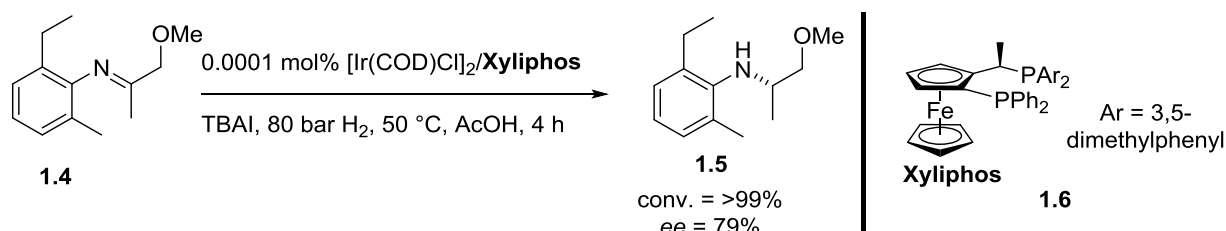
1.1

$\xrightarrow[\text{MeOH, RT, 2 h}]{0.5 [\text{Rh}(\text{COD})\text{Cl}]_2 + \text{L}^*, 1 \text{ bar H}_2}$

1.3

Entry	$\text{P}_{cis}$	$\text{P}_{trans}$	Catalyst loading [mol%]	Conv. [%]	<i>Ee</i> [%]
1	$\text{PPh}_2$	$\text{PPh}_2$	0.1	36	5
2	$\text{P}(p\text{-Me}_2\text{NPh})_2$	$\text{PPh}_2$	0.1	55	68
3	$\text{PPh}_2$	$\text{P}(p\text{-Me}_2\text{NPh})_2$	0.1	>99	93

Although these results emphasize the potential advantages of electronically and sterically unsymmetrical ligands, this approach does not guarantee an improved catalyst performance. If isomeric complexes are formed, in which the two phosphine groups have switched positions, all efforts to optimize the coordinating groups individually can be pointless. However, in the absence of such complications the catalyst performance can be impressive as in the case of the industrial production of (*S*)-metolachlor.<sup>[15]</sup> Applying the  $C_1$ -symmetric Xyliphos ligand (**1.6**), the catalyst reached more than  $10^6$  turnovers and  $10^5$  turnovers per hour (scheme 1.1).

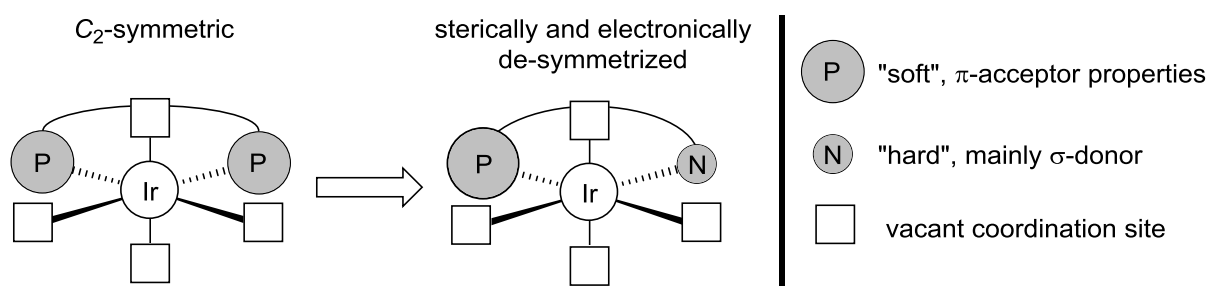
**Scheme 1.1:** Asymmetric hydrogenation as key step in the production of (*S*)-metolachlor.

### 1.3 Synthesis and further development of chiral ligands enabling the hydrogenation of C=C bonds by iridium-based catalysts

The range of prochiral olefins that can be hydrogenated with high enantiomeric excess is still limited using both rhodium- and ruthenium-based catalysts. Such complexes require the presence of a coordinating functional group adjacent to the C=C bond. For this reason dehydro-amino acid derivatives or allylic alcohols are frequently found as suitable substrates

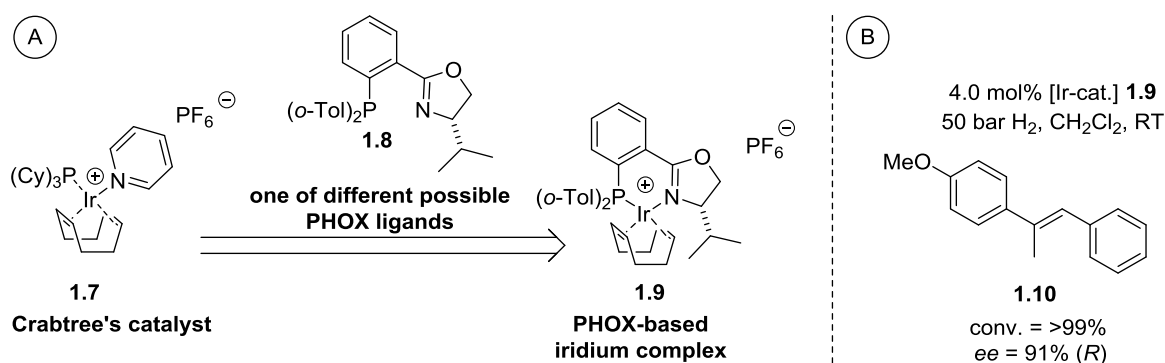
for these catalysts. On the other hand olefins lacking coordinating groups normally show poor results as substrates for rhodium- or ruthenium-catalyzed asymmetric hydrogenations.

One key step to significantly broaden the substrate scope for asymmetric hydrogenation was the development of mixed N,P ligands. Such ligands represent an even more effective way of desymmetrization, based on the different electronic nature of P and N atoms. These bidentate ligands contain a “soft” P-ligand with  $\pi$ -acceptor properties and a “hard” N-ligand with mainly  $\sigma$ -donator character (figure 1.5).



**Figure 1.5:** Desymmetrization by different coordinating heteroatoms.

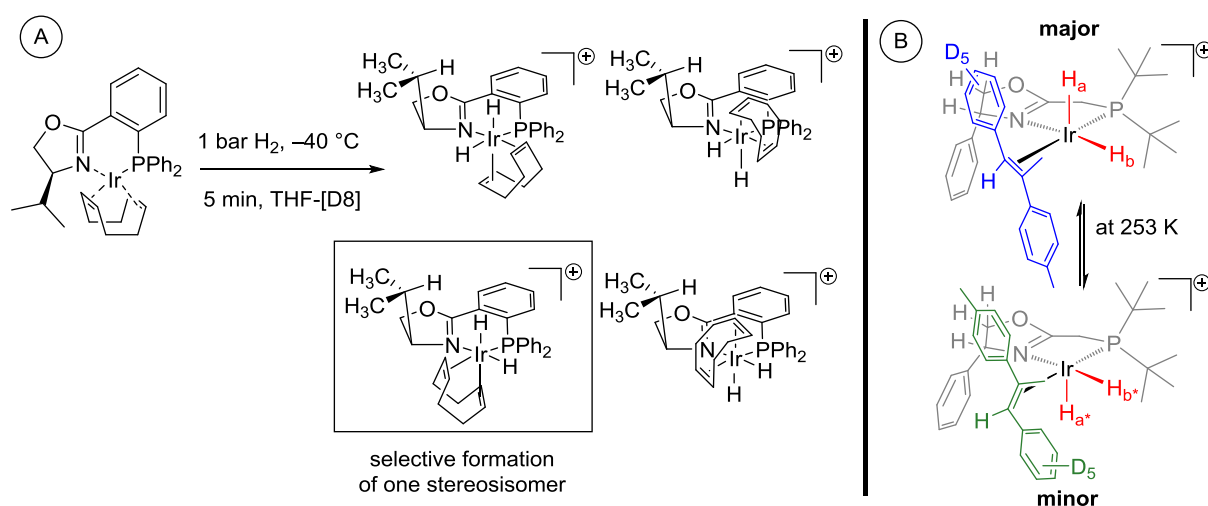
The first ligands of this type were phosphinooxazoline ligands (PHOX) and were introduced in 1993 in three independent publications from the laboratories of Helmchen, Pfaltz and Williams.<sup>[16]</sup> PHOX ligands were successfully used for asymmetric palladium-catalyzed allylic substitution and later on for many different reactions.<sup>[17]</sup> In 1998 the potential of this ligand class for the asymmetric hydrogenation of unfunctionalized olefins was demonstrated. Inspired by Crabtree's catalyst (**1.7**),<sup>[18]</sup> which showed high reactivity in the hydrogenation of unfunctionalized C=C bonds, Ir complexes derived from PHOX ligands such as **1.8** were tested in the asymmetric hydrogenation of olefins and found to give encouraging results (scheme 1.2, A and B).<sup>[19]</sup>



**Scheme 1.2:** PHOX-based iridium complex as catalyst in the hydrogenation of unfunctionalized olefins.

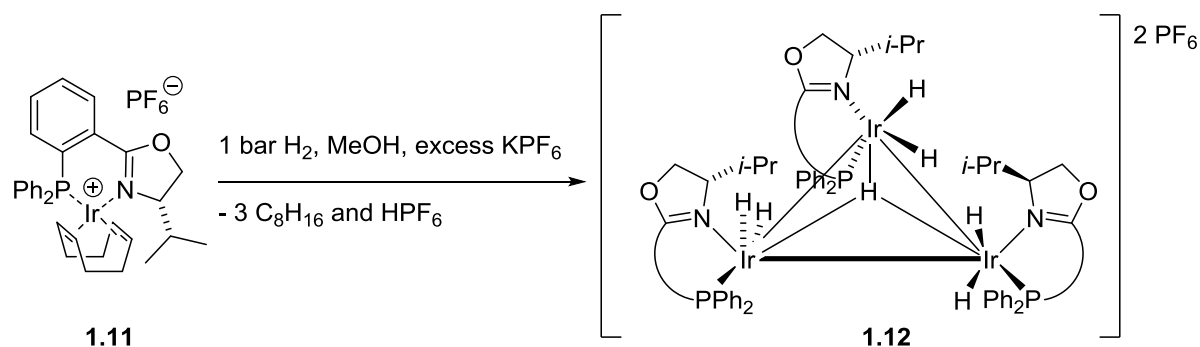


By  $^1\text{H}$  NMR experiments conducted at low temperature it was possible to demonstrate that out of the four possible stereoisomers formed upon oxidative addition of dihydrogen, exclusively one stereoisomer was obtained due to electronic and steric differentiation (scheme 1.3, A).<sup>[20]</sup> Most recently it was even possible to characterize dihydride intermediates with a coordinated alkene, representing the resting state of the catalyst (scheme 1.3, B).<sup>[21]</sup> These findings show that the electronic discrimination of the N,P ligand results in the oxidative addition of hydrogen exclusively *trans* to the Ir–N bond, which is electronically favored.<sup>[22]</sup> This orientation of the hydrides leaves a free coordinating side *trans* to the Ir–P bond and therefore, in agreement with computational studies,<sup>[23]</sup> also determines the coordination of the substrate in *trans* position to the phosphorous atom.



**Scheme 1.3:** Selective formation of specific iridium dihydride species due to electronic and steric differentiation.

But not only the electronic nature of the catalyst proved to have a crucial effect on the performance of such complexes, a major influence had also to be ascribed to the counterion of these complexes. The first results obtained with iridium complexes derived from chiral PHOX ligands showed encouraging results in the hydrogenation of *trans*-methyl stilbene derivative **1.10**. Applying 50 bar hydrogen pressure, the product **1.13** was obtained in up to 91% *ee* and >99% conversion (scheme 1.2, B).<sup>[19]</sup> However, lower catalyst loadings than 4 mol% resulted in decreased conversion. Kinetic studies conducted showed an initial high turnover frequency of  $7200\text{ h}^{-1}$  and full conversion was achieved within less than 1 min.<sup>[24]</sup> Apparently, deactivation seemed to be a serious problem for these catalysts. Investigations aimed at solving this issue revealed the formation of the inactive trinuclear iridium hydride cluster **1.12** (scheme 1.4),<sup>[25]</sup> in analogy to the deactivation products observed for Crabtree's catalyst.<sup>[26]</sup> All attempts to regenerate the catalytic active species from trimer **1.12** failed.<sup>[25]</sup>



**Scheme 1.4:** Formation of trinuclear iridium hydride species as main deactivation pathway of catalysts.

Efforts to increase conversion by variation of reaction parameters such as solvent, concentration or hydrogen pressure were unsuccessful. The solution to this problem was as simple as surprising. The exchange of the counterion from  $\text{PF}_6^-$  to tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ( $\text{BAr}_\text{F}^-$ ) showed significantly increased conversion. Applying the  $\text{PF}_6^-$  and the  $\text{BAr}_\text{F}^-$  salt of the identical PHOX-derived iridium complexes in the hydrogenation the *trans*-methyl stilbene derivative **1.10** resulted in more than 10 times higher conversion in the case of the  $\text{BAr}_\text{F}^-$  salt (table 1.2).

**Table 1.2:** Enantioselective hydrogenation of *trans*-methyl stilbene derivative **1.10** with PHOX-based iridium catalyst bearing different counterions.

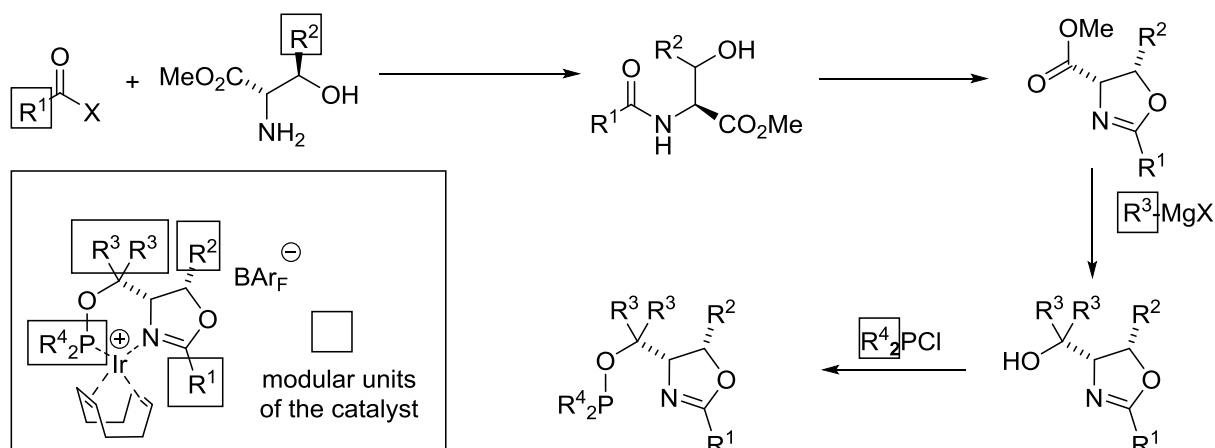
Entry	Counterion	Catalyst loading [mol%]	Conv. [%]	<i>Ee</i> [%]
1	$\text{PF}_6^-$	4.0	78	75
2	$\text{BAr}_\text{F}^-$	0.3	>99	70

The reason for such behavior is not obvious but comparative kinetic experiments conducted with iridium complexes bearing different counterions provided a plausible answer to this question.<sup>[27]</sup> Catalysts with  $\text{PF}_6^-$  as counterion showed first order rate dependence on the olefin concentration whereas for catalysts containing  $\text{BAr}_\text{F}^-$  as counterion the rate was close to zero order.

The observed difference may be explained by the stronger coordination ability of the  $\text{PF}_6^-$  counterion or the formation of a tighter ion pair compared to  $\text{BAr}_\text{F}^-$ , that therefore slows down

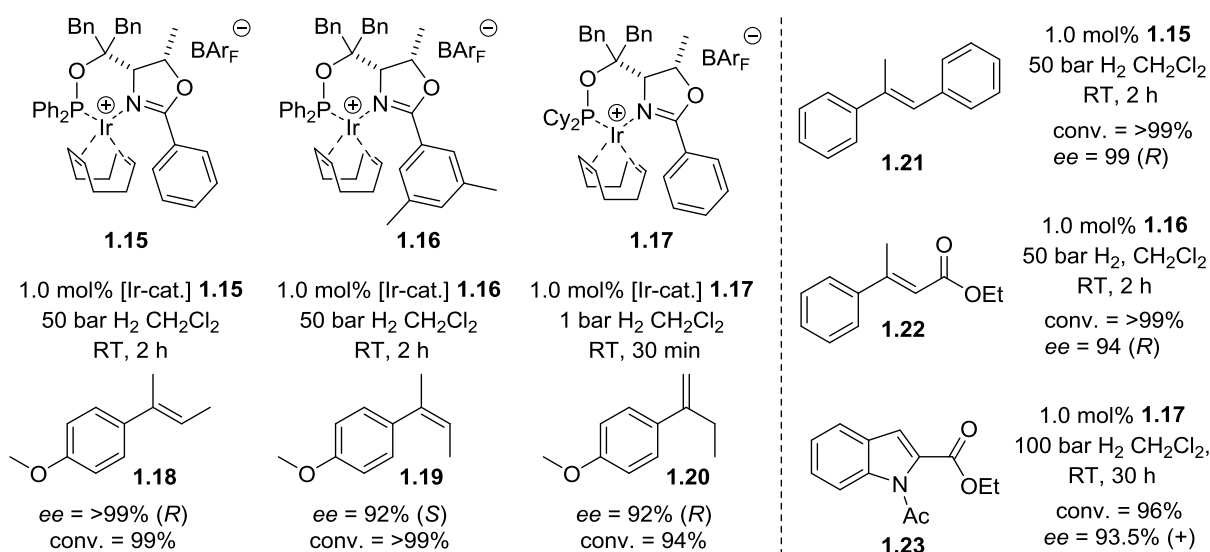
the coordination of the olefin to the metal center of the catalyst. As result the addition of the olefin to the metal center becomes rate-determining. In contrast, the bulky and very weakly coordinating  $\text{BAr}_\text{F}$  does not hamper olefin coordination, which means that the metal center remains “saturated” with substrate. Taking in account that the structure of the trinuclear cluster is responsible for catalyst deactivation, the lower reactivity of  $\text{PF}_6$  salts with the olefin should favor the formation of such trinuclear clusters starting from an iridium hydride species with a vacant coordination site. In addition to the higher conversion obtained with  $\text{BAr}_\text{F}$ -based iridium complexes, the exchange of the counterion resulted in catalysts that were significantly easier to handle. In fact, these complexes are stable against moisture and oxygen and therefore can be easily handled in air, whereas  $\text{PF}_6$ -based complexes required handling under inert gas atmosphere. Furthermore, it is possible to purify iridium- $\text{BAr}_\text{F}$  complexes by column chromatography on silica gel if necessary which facilitates the purification of catalysts significantly.

After these first reports the number of chiral N,P ligand complexes for the asymmetric hydrogenation of  $\text{C}=\text{C}$  bonds continuously increased. Because of the limited mechanistic insights at this time the synthesis of new ligand classes relied on empirical approaches. Therefore, most of the ligands applied in the iridium catalyst asymmetric hydrogenation were found by chance, intuition or systematic screening. To facilitate the finding of new efficient catalysts by systematic screening, ligands revealing a high modular structure emerged as desirable targets. One of such modular ligand structures, is derived from the amino acids serine or threonine.<sup>[28]</sup> In contrast to the first PHOX ligands, a phosphinite is attached to the stereogenic center of the catalyst, being part of the six-membered chelate ring. Overall this ligand class contains four structural elements, which can be modified in a four step reaction sequence, employing different carboxylic acid derivatives, chlorophosphines and Grignard reagents (scheme 1.5).



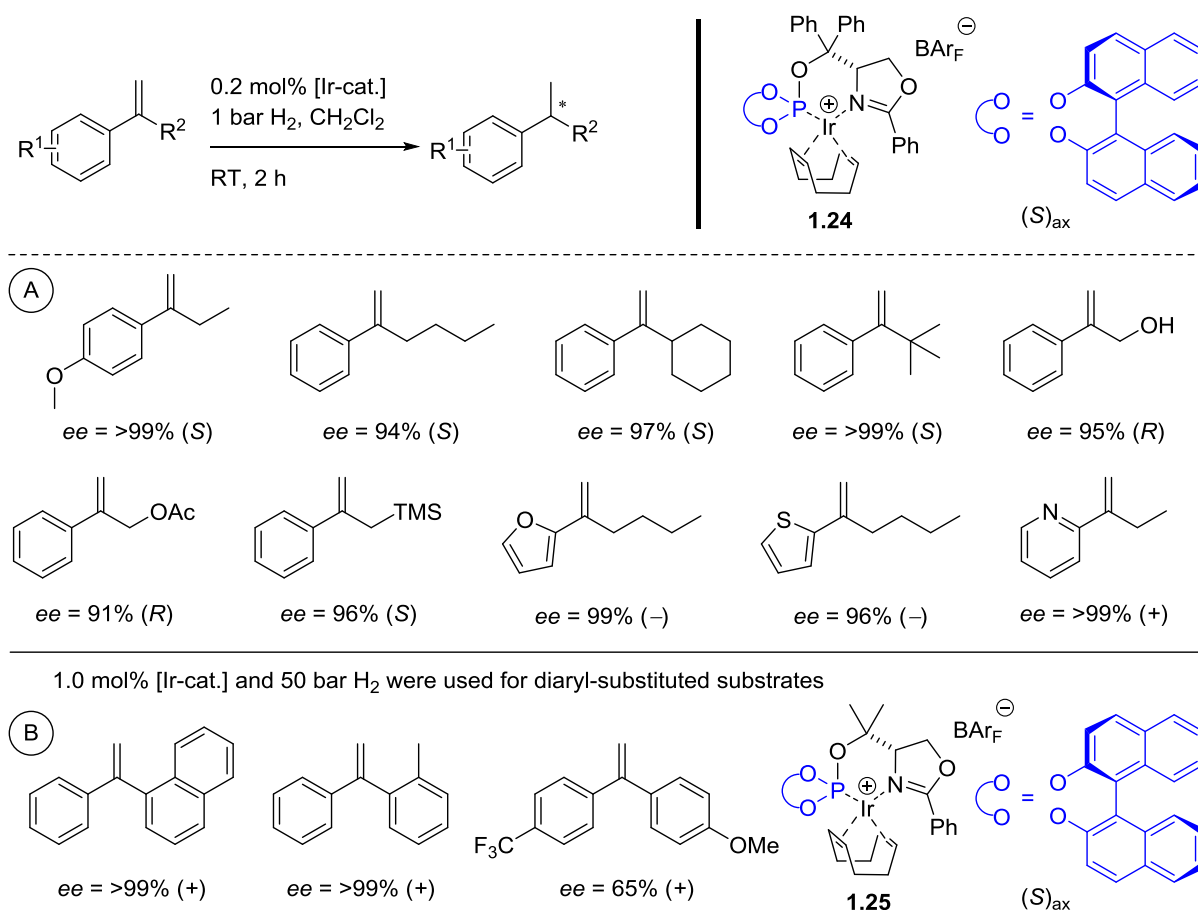
**Scheme 1.5:** Modular synthesis of SerPHOX and ThrePHOX ligands.

The high modularity of this ligand structure allowed for the preparation of a diverse library of chiral iridium complexes. The effectiveness of this approach was nicely demonstrated using the three olefins **1.18**, **1.19** and **1.20**, representing different isomers at the C=C bond, which provide after hydrogenation the same product. In this case, a different catalyst performed best for each substrate and high enantiomeric excesses between 94 and >99% were obtained (scheme 1.6). The fact that these catalysts showed high selectivity in the hydrogenation of many different substrates such as **1.21**, **1.22** and **1.23** highlights the importance of the modular approach for catalyst synthesis and helped to further broaden the substrate scope compared to the previously discussed PHOX-based iridium complexes.<sup>[28b, 29]</sup>



**Scheme 1.6:** Different ThrePHOX-based iridium catalysts achieving high selectivity in the hydrogenation of different substrates.

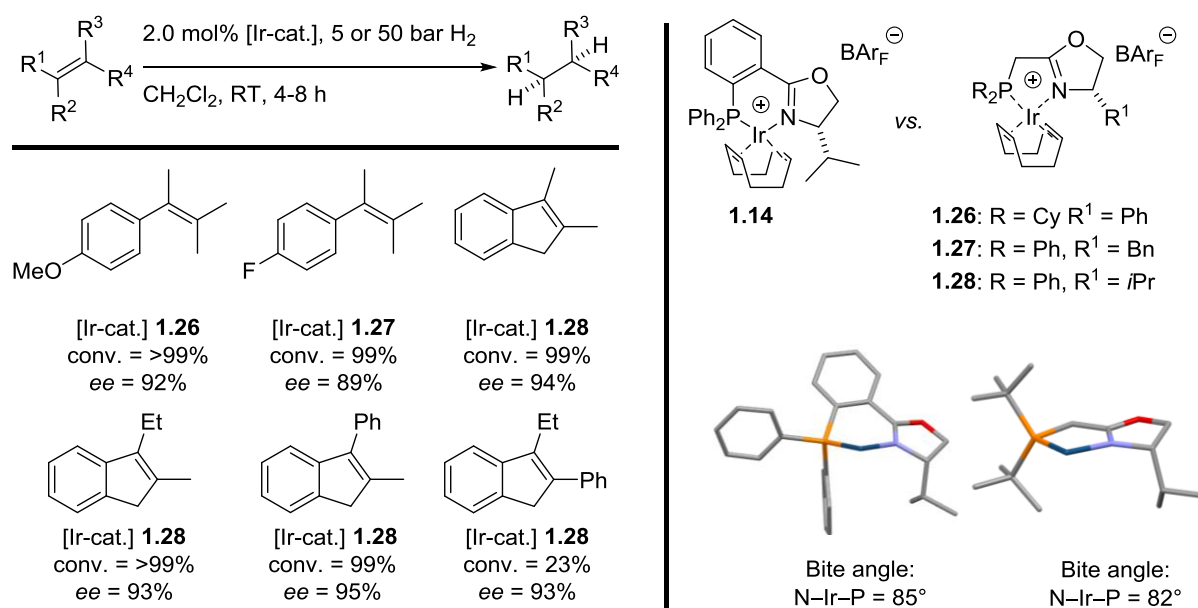
Although reasonably high enantioselectivity for substrate **1.20** (92% *ee*) was obtained using iridium catalyst **1.17**, in general terminal olefins remained challenging substrates in terms of enantioselectivity compared to trisubstituted ones. The difficulty arises from the fact that these substrates contain only two substituents, and these are responsible for the discrimination between the two enantiofaces of the C=C bond. Furthermore, terminal olefins with  $\alpha$  hydrogen atoms next to the double bond are known to undergo a competitive isomerization under hydrogenation conditions to the thermodynamically more stable trisubstituted isomers.<sup>[30]</sup> However, the hydrogenation of the corresponding trisubstituted isomers can result in the product with opposite configuration. In order to overcome these issues, Andersson and co-workers prepared a library containing 96 different phosphite-oxazoline ligands. By systematic variation of different residues on the ligand scaffold of catalyst **1.24**, axial chiral biarylphosphites were found to be highly beneficial in the hydrogenation of 1,1 disubstituted alkenes.<sup>[30-31]</sup> These ligands allowed for the hydrogenation of a wide range of different 1,1 disubstituted alkenes containing one aromatic substituent on the C=C bond (scheme 1.7, A). Unfunctionalized terminal olefins were hydrogenated with up to >99% *ee*. In addition, the presence of neighboring groups such as hydroxyl, acetate, silane or heteroaryls were tolerated as well and *ees* between 91 and 99% were obtained. Furthermore, catalyst **1.25** showed good to excellent results in the hydrogenation of sterically and electronically diverse terminal biaryl alkenes. For example, the terminal olefin consisting of a phenyl and a *ortho*-tolyl substituent on the double bond was reduced with up to >99% *ee*. In the case of electronically different aryl substituents like *para*-trifluoromethylphenyl and a *para*-methoxyphenyl a promising result (65% *ee*) was obtained (scheme 1.7, B).



**Scheme 1.7:** Hydrogenation of terminal olefins with oxazoline-based catalyst bearing an axial chiral biarylphosphite moiety. Full conversion was observed for all entries.

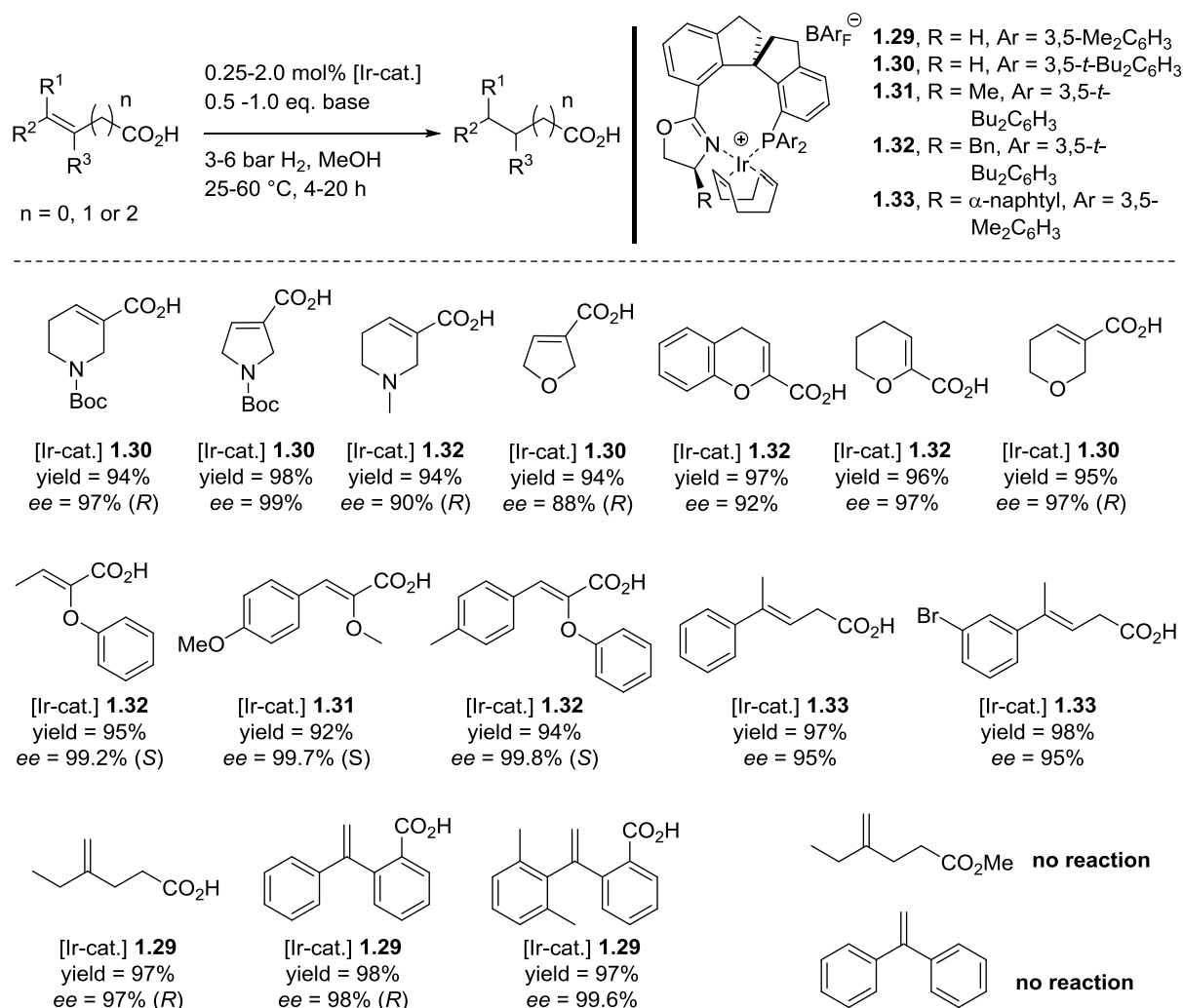
All previously introduced complexes emerged as efficient catalysts for the hydrogenation of trisubstituted and terminal olefins. However, they all performed poorly in the hydrogenation of tetrasubstituted olefins. Such a limitation can be explained by the increased steric demand of tetrasubstituted olefins compared to trisubstituted ones. Tetrasubstituted alkenes have been successfully hydrogenated by Buchwald and co-workers using chiral zirconocene complexes. However, long reaction times, high pressure and high catalysts loadings are drawbacks of these systems.<sup>[32]</sup> Encouraging results for tetrasubstituted alkenes were observed by the application of the easily accessible phosphanyl oxazoline ligands, first reported by Spritz and Helmchen for allylic substitution reactions.<sup>[16a]</sup> The corresponding iridium complexes achieved high enantioselectivities and high conversion for tetrasubstituted substrates that possess at least one methyl substituent (scheme 1.8).<sup>[33]</sup> For more sterically demanding substrates also these catalyst showed reduced reactivity. A reasonable explanation for the higher reactivity of phosphanyl oxazoline-derived iridium complexes might originate from the formation of a 5-membered chelate ring with the metal center rather than a 6-membered chelate ring which is typical of the previously discussed complexes. A smaller chelate ring

between the ligand and the metal center results in a smaller bite angle and a subsequent easier access of the substrate to the metal.



**Scheme 1.8:** Phosphanyl oxazoline-derived iridium catalysts in the hydrogenation of tetrasubstituted unfunctionalized olefins. (The BAr<sub>F</sub><sup>−</sup> counterions and the COD-ligand were omitted for clarity).

In contrast to the previously discussed iridium complexes, reports on ligands forming larger chelate rings constantly increased in the last years and the resulting catalysts showed promising results in the hydrogenation of different substrate classes. Especially worth mentioning are the SIPHOX-based iridium catalysts developed Zhou and co-workers, bearing an extremely rigid axially chiral spirobiindane backbone. These catalysts showed remarkable selectivities in the hydrogenation of a wide variety of different unsaturated carboxylic acids. Furthermore, the applied reaction conditions with methanol as solvent and a base as additive were quite unique for iridium-based catalysts. Normally asymmetric hydrogenation with iridium-based catalysts are performed in weakly coordinating solvent such as CH<sub>2</sub>Cl<sub>2</sub> or toluene.<sup>[34]</sup> Coordinating solvents or additives, such as methanol or triethylamine are known to significantly reduce catalyst reactivity.<sup>[35]</sup> Nevertheless, the substrate scope of the SIPHOX-based catalysts is remarkably broad in the presence of a coordinating solvent and a base (scheme 1.9), as unsaturated heterocyclic acids,<sup>[36]</sup> α-aryloxy and α-alkoxy α,β-unsaturated carboxylic acids,<sup>[37]</sup> β,γ-unsaturated carboxylic acids<sup>[38]</sup> or terminal double bonds with a carboxylic acid in the β-position were successfully hydrogenated.<sup>[39]</sup> In all these examples the coordination of the carboxylate to the metal center proved to have a crucial effect on the catalyst reactivity. Unfunctionalized olefins or the analogous carboxylic esters showed no reactivity in the hydrogenation with these catalysts.

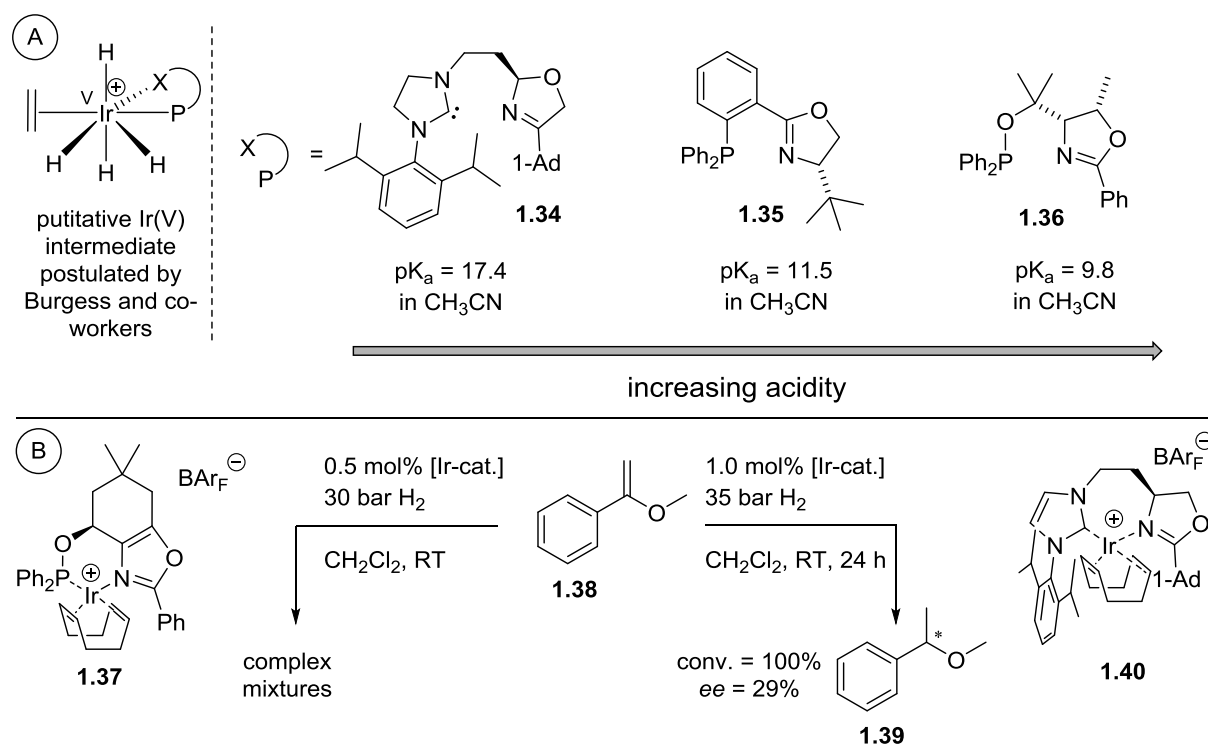


**Scheme 1.9:** Iridium SIPHOX-based catalyst in the asymmetric hydrogenation of  $\alpha,\beta$ -unsaturated carboxylic acids.

As demonstrated by the previous two examples the size of the chelate ring can have a significant influence on the catalyst performance. So far the focus was set on N,P ligands which are not the only ligand class successfully used in the iridium-catalyzed asymmetric hydrogenation. Another class originally developed by Burgess and co-workers are C,N ligands. In this case the phosphorous unit is replaced by a N-heterocyclic carbene.<sup>[40]</sup> This exchange resulted in iridium complexes with different electronic properties on the metal center, which turned out to be highly advantageous for acid-labile substrate. During the course of the reaction different iridium hydride species are formed, containing hydrides with different acidity. DFT calculations of putative Ir(V)-hydride intermediates in the catalytic cycle predicted that iridium N,P ligand complexes can form hydrides being up to 7.6 pK<sub>a</sub> units more acidic than the corresponding C,N intermediates (scheme 1.10, A).<sup>[41]</sup> These calculations were supported by experimental observations. For example the enol ether **1.38** was converted



selectively to the desired product **1.39** in the presence of the C,N ligand-based iridium complex **1.40**,<sup>[42]</sup> whereas N,P ligand-based iridium complex **1.37** resulted in the formation of a complex reaction mixture (scheme 1.10, B).<sup>[43]</sup> Also other substrates containing acid-labile groups such as TMS-ethers or *tert*-butyl carboxylic esters were hydrogenated with superior results using C,N instead of N,P ligand-based iridium catalysts.<sup>[44]</sup>

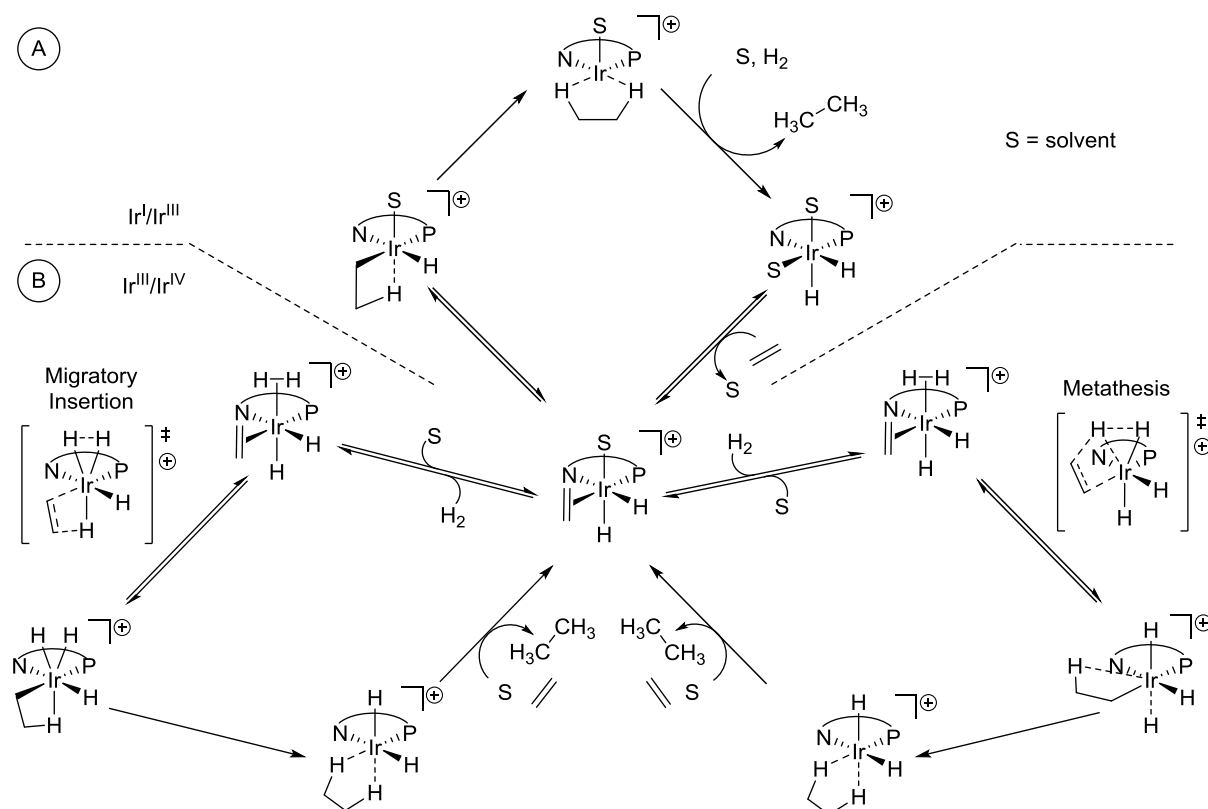


**Scheme 1.10:** Iridium C,N ligand-based complexes as superior catalysts for substrates containing acid-labile groups.

## 1.4 Mechanistic studies and deviation of a model for the enantioselective step

Despite the vast amount of literature on iridium-catalyzed asymmetric hydrogenations and the remarkable progress on ligand development over the last years, the mechanism of this transformation is not completely understood so far. Current mechanistic proposals by Andersson and co-workers and Burgess and co-workers are almost entirely based on DFT calculations which support a catalytic cycle starting from iridium(III) intermediates (scheme 1.11, B).<sup>[45]</sup> On the other hand experiments conducted by Chen and Dietiker, based on electrospray ionization tandem mass spectrometry, suggest an  $\text{Ir}^{\text{I}}/\text{Ir}^{\text{III}}$  cycle,<sup>[46]</sup> analogous to the well-established mechanism for rhodium-catalyzed hydrogenation (scheme 1.11 A).<sup>[47]</sup>

Nevertheless, these experiments which were conducted in the gas phase do not rule out a  $\text{Ir}^{\text{III}}/\text{Ir}^{\text{VI}}$  cycle in solution.<sup>[46]</sup> Recent experimental studies, where a  $[\text{Ir}^{\text{III}}(\text{H})_2(\text{alkene})(\text{L})]^+$  intermediate was obtained and characterized at low temperature (for details see scheme 1.3), showed that additional  $\text{H}_2$  is required to enable hydrogen addition to the alkene upon warming.<sup>[21]</sup> These experimental data support an  $\text{Ir}^{\text{III}}/\text{Ir}^{\text{V}}$  cycle *via* an  $[\text{Ir}^{\text{III}}(\text{H})_2(\text{alkene})(\text{H}_2)(\text{L})]^+$  intermediate, as originally proposed by Andersson and co-workers.

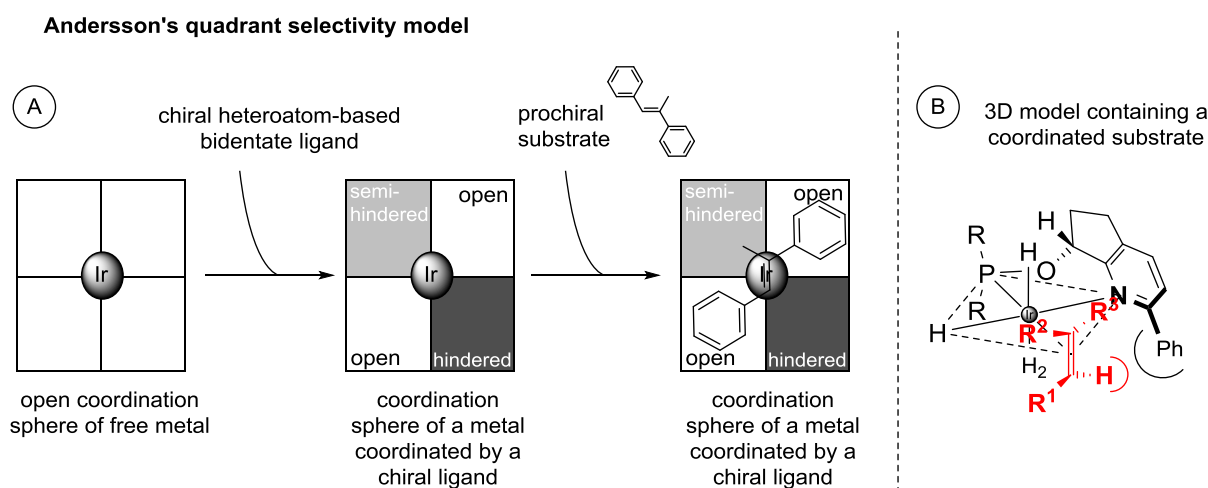


**Scheme 1.11:** Different catalytic cycles proposed for iridium-catalyzed asymmetric hydrogenation.

So far mechanistic considerations had only limited influence on the design and development of new catalysts and were mainly used to explain results after the fact. Given the high fluxionality, multifaceted aggregation behavior of iridium hydride complexes and high reactivity of different iridium hydride species, it will remain a significant challenge if not an impossible task to rationally design new ligands. Furthermore, it cannot be ruled out that the mechanism differs depending on the reaction conditions, the catalyst or on the substrates used. For example, substrates with an additional coordinating group should disfavor coordination of a second hydrogen molecule that would be essential for the formation of an Ir(V)-intermediate. Perhaps under certain reaction conditions different pathways could operate in parallel.

Regardless of the full mechanistic picture, the essential part of enantioselective reactions is the enantiodiscriminating step. Based on DFT calculations, Brandt and Andersson proposed a qualitative model that predicts the enantiofacial selectivity of iridium-based catalysts.<sup>[48]</sup> As depicted in scheme 1.12, the ligand forms a chiral pocket around the metal center. One part of the ligand, as for example in scheme 1.12, B, the phenyl group, points out of the plane, and sterically interacts with the substrate, which is bound *trans* to the P atoms. This steric interaction favors a coordination geometry, in which the smallest substituent of the C=C bond, the H atom, is positioned in the hindered quadrant. The substituents at the phosphorus atom cannot generate direct steric interaction with the substrate, due to the long distance. However, the residues on the phosphorous atom can still influence the enantioselectivity by electronic effects as well as steric effects by interaction with axial ligands and the backbone of the ligand, as depicted in scheme 1.12, B.

This model can be used to predict the absolute configuration of the product for a wide range of hydrogenations, by the identification of the hindered quadrant and placing the least sterically demanding substituent of the substrate in this position to minimize steric repulsion. In this case, the substrate is bound with the enantioface resulting in the formation of the experimentally observed product. However, this model has to be used with caution. In substrates with a strongly polarized C=C bond such as  $\alpha,\beta$ -unsaturated carboxylic esters, electronic effects can override steric interactions resulting in a break-down of the model.<sup>[49]</sup>

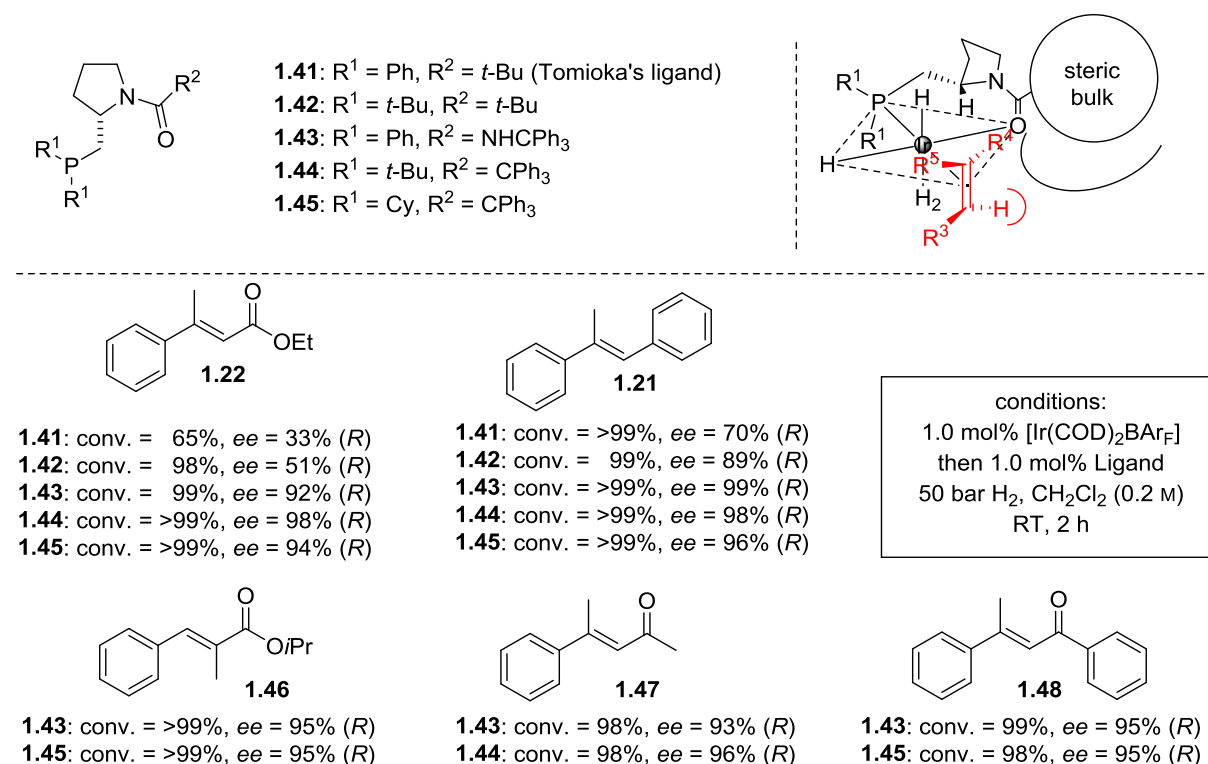


**Scheme 1.12:** Andersson's quadrant model developed to rationalize the enantioselectivity.

In addition, this model predicts how the substrate interacts with the catalyst and therefore enables a semi-rational approach to improve ligands. Taking into account that mainly one part of the ligand is involved in steric repulsion with the substrate, this group should significantly

affect the outcome of the reaction. A large substituent should result in a more congested environment around the metal center of the catalyst and therefore form a tighter chiral pocket. On the other hand, if this group is too sterically demanding, reduced reactivity and enantioselectivity should be observed. In chapter 2 experiments confirming these predictions are presented.

Another bidentate ligand structure, for which this model was successfully used for optimization, is shown in scheme 1.13. In this work O,P ligands based on a proline scaffold were applied to the asymmetric hydrogenation of functionalized and unfunctionalized olefins. These ligands were developed starting with a broad automated screening of various metal-ligand combinations, which revealed for Tomioka's ligand<sup>[50]</sup> (**1.41**) 68% *ee* in the hydrogenation of (*E*)-1,2-diphenylprop-1-ene.<sup>[51]</sup> This ligand can be easily obtained starting from proline and forms a seven-membered chelate ring with the metal center. In line with the model shown in scheme 1.12 for systematic variation of the residues ( $R^2$ ), higher *ee* values were obtained by increasing the size of the amide or urea group. For example in the hydrogenation of ethyl (*E*)-3-phenylbut-2-enoate (**1.22**) the enantiomeric excess was raised from 33% up to 98%, by increasing the steric bulk of the ligand. Moreover, also for many other substrates, catalysts containing a sterically more demanding  $R^2$  group showed high *ee* values (scheme 1.13).



**Scheme 1.13:** Proline-based iridium complexes as catalysts in the hydrogenation of different substrates.

## 1.5 Conclusion

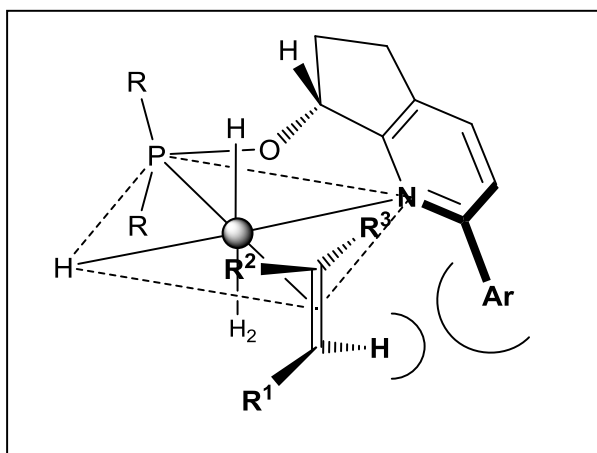
Since the first successful report in 1998, the iridium-catalyzed asymmetric hydrogenation of alkenes emerged as a method to introduce new stereogenic centers to a broad variety of different functionalized and unfunctionalized prochiral olefins in a highly selective manner. The key factor to success was the application of hetero-bidentate ligands with two coordinating atoms exhibiting different electronic properties. Initially ligand development was conducted empirically by systematic screening of highly modular ligand scaffolds. The modularity of new ligands emerged as an important feature to achieve high enantioselectivities for a wide range of derivatives of a certain substrate classes, because minor changes in the substrate can significantly affect the selectivity of the reaction.

Although progress has been made in the mechanistic understanding of the Ir catalysis, much further work will be necessary to reach the level allowing truly rational catalyst design based on mechanistic considerations. Moreover, despite the large number of Ir catalysts developed so far, there are still important substrate classes such as dienes or heterocyclic compounds for which generally applicable hydrogenation catalysts are lacking. The goal of this thesis was to develop new catalysts and improved hydrogenation for challenging substrate classes that so far had given unsatisfactory results.



## Chapter 2

### Development and Study of Pyridine-Phosphinite-Based Catalysts with a Sterically Demanding Aryl Substituent



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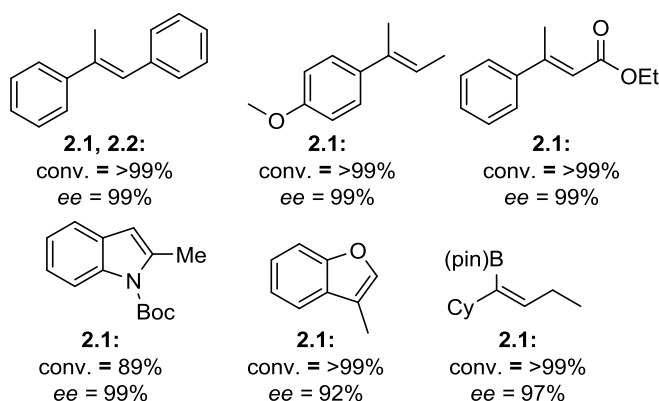


## 2.1 Introduction

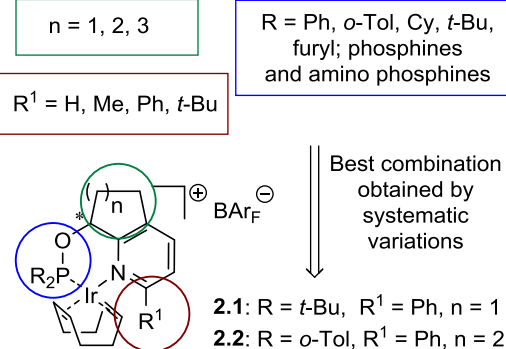
As discussed in the previous chapter, the continuous development of known catalysts and ligands can lead to significantly improved results in the asymmetric hydrogenation of unfunctionalized olefins. One class of iridium-based catalysts which was not discussed in the first chapter is the one based on bicyclic pyridine-phosphinite ligands. These complexes are among the most successfully applied catalysts in the hydrogenation of unfunctionalized olefins.<sup>[52]</sup> They resemble chiral versions of Crabtree's catalyst,<sup>[18]</sup> as they consist of a pyridine moiety which is bridged by a cyclic aliphatic backbone to a phosphinite unit, forming a six-membered chelate ring with the metal center. Remarkable selectivity was observed in the hydrogenation of different functionalized and unfunctionalized olefins and also for complex intermediates in key steps of several total syntheses (Figure 2.1).<sup>[29b, 53]</sup> Therefore, these iridium-based complexes belong to the small group of catalysts which showed their applicability to a broad substrate range.

Several systematic variations have been investigated to optimize the ligand structure of these catalysts on different positions. Five-, six- and seven-membered aliphatic rings were employed in the backbone of the catalyst. Different phosphinite groups, with phenyl, *ortho*-tolyl, furyl, cyclohexyl and *tert*-butyl residues were tested as well as phosphines and amino phosphines. Furthermore, the influence of different substituents at the 2-position of the pyridine moiety was investigated. A methyl and a phenyl group showed a significant influence on the selectivity compared to a hydrogen atom at this position. It should be mentioned, that larger groups such as a *tert*-butyl group were also applied, but they are not tolerated in this position, probably because strong steric hinderance inhibited coordination to the metal center.<sup>[52, 54]</sup> Out of several different combinations, two catalysts were identified to perform better overall: Catalyst **2.1**, bearing a di-*tert*-butyl phosphinite, a five-membered ring in the backbone, and a phenyl group at the 2-position of the pyridine, and catalyst **2.2**, containing a di-*ortho*-tolyl-phosphinite, an aliphatic six-membered ring in the backbone and also a phenyl group on the pyridine. Among other examples, these catalysts have been successfully applied in the hydrogenation of the vitamin E precursor,  $\gamma$ -tocotrienyl acetate, which allowed for the hydrogenation of three double bonds and the introduction of two stereogenic centers in one step. In the case of catalyst **2.2** >98% of the natural (*R,R,R*)-isomer of  $\gamma$ -tocopheryl acetate was obtained.<sup>[53c]</sup>

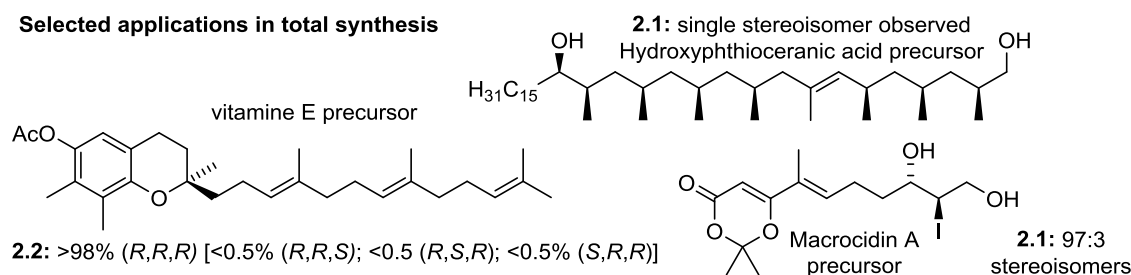
## Selected test substrates and substrate classes



## Modifications conducted on the ligand scaffold

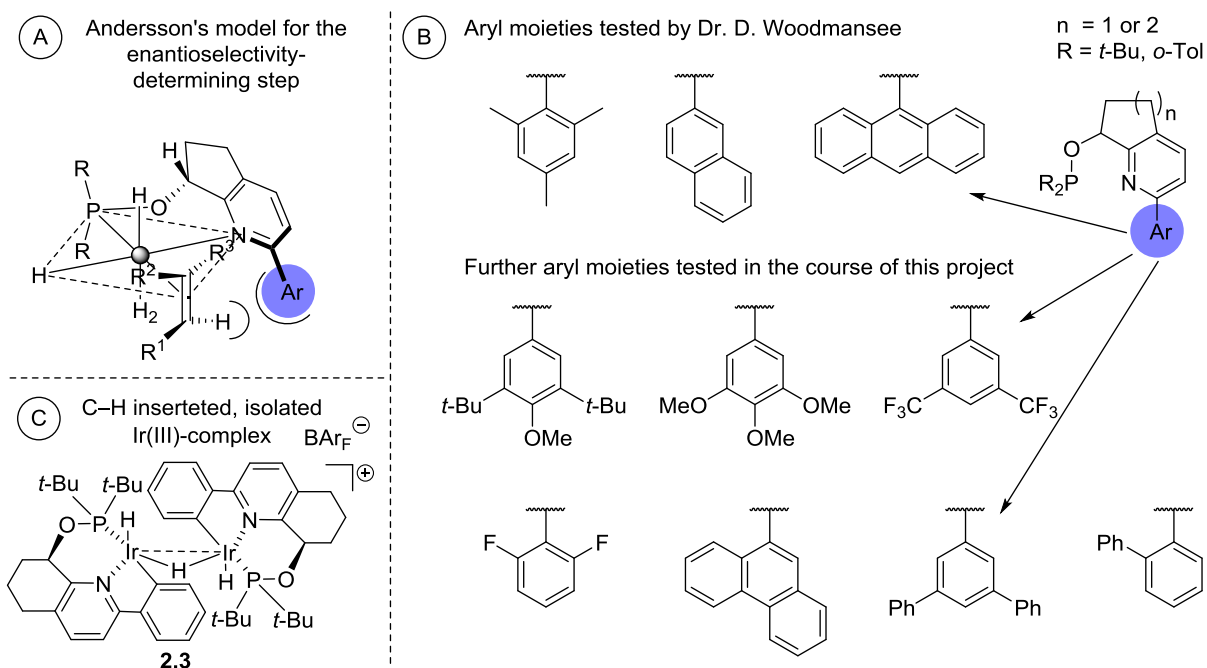


## Selected applications in total synthesis



**Figure 2.1:** Different selected substrate classes and intermediates in total synthesis successfully hydrogenated by the use of the most efficient catalysts of this series **2.1** and **2.2**.

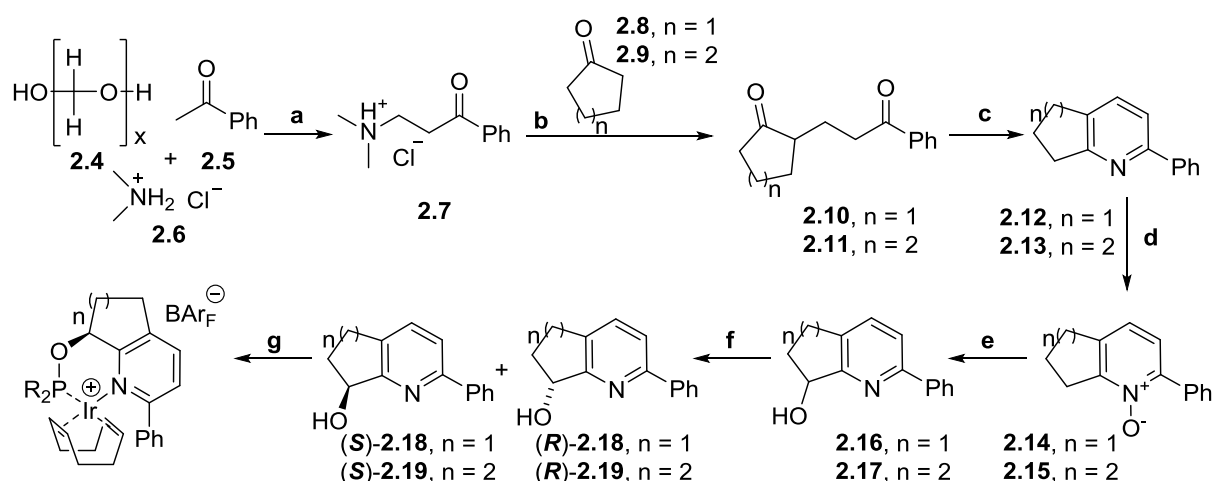
However, there is still room for improvement, which could lead to a further broadening of the substrate scope. Based on the already discussed model for the enantioselectivity-determining step developed by Andersson and co-workers, it can be presumed that the aryl moiety of this catalyst should have a significant influence on the enantioselectivity of the hydrogenation (figure 2.2, A). Therefore, the idea was to introduce sterically demanding aryl groups at the 2-position of the pyridine moiety, which should generate a more congested environment around the metal center of the catalyst (figure 2.2, B). In addition, it is known for iridium complexes that they can undergo an insertion into an adjacent aromatic C–H bond, which was found to be a facile process for 2-phenylpyridines.<sup>[55]</sup> Such behavior was also observed by Dr. Andreas Schumacher who was able to isolate the C–H inserted Ir(III)-complex **2.3** formed from its COD precatalyst in the absence of a substrate under hydrogen atmosphere (figure 2.2, C). Therefore, an introduction of a substituent in *ortho*-position should block a potential C–H activation, or sterically more demanding substituents in *meta*-position could favor an orientation which might impede the C–H insertion. This project was started by Dr. David Woodmansee in the course of his PhD thesis in which the influence of mesityl, 2-naphthyl and 9-antraceny groups was tested. Based on the preliminary success obtained with the new catalysts, it was decided to further investigate this part of the ligand.



**Figure 2.2:** Andersson's model for the enantioselectivity-determining step, A; The different aryl groups tested at the 2-position of the pyridine moiety, B; C-H inserted Ir(III)-complex obtained in the absence of a substrate under hydrogen atmosphere.

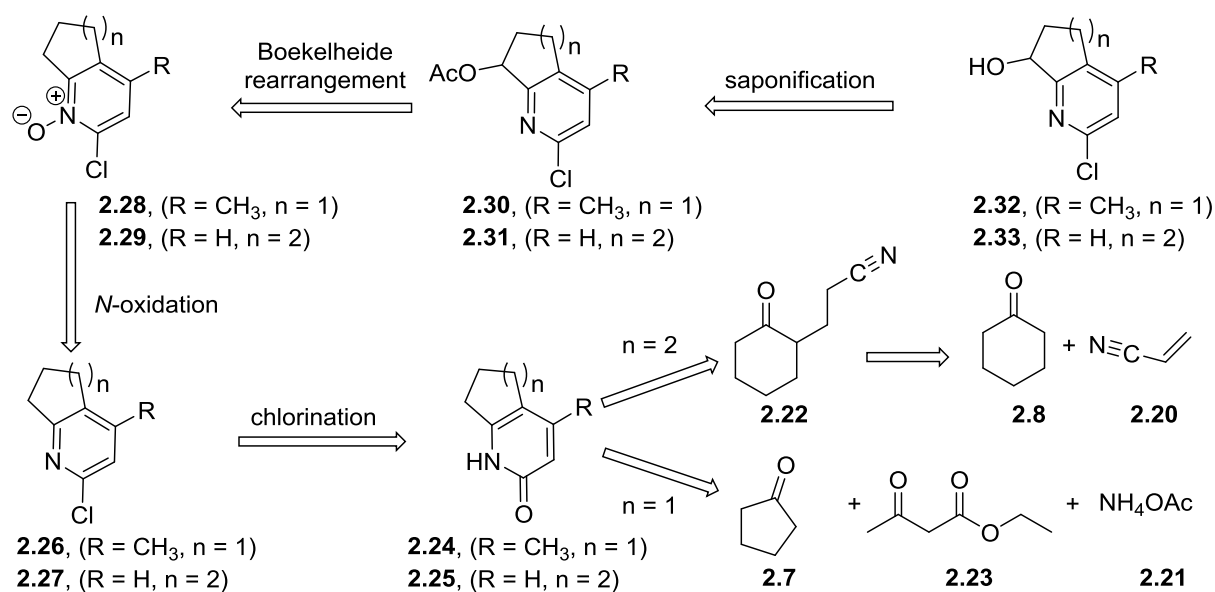
## 2.2 Catalyst Synthesis

The original synthesis of the catalysts bearing a phenyl group was in the meanwhile intensively investigated and thus can be achieved efficiently. However, the phenyl group is introduced in the very first step of the synthesis by a Mannich reaction using acetophenone (**2.5**) and therefore this route is not practical for the fast synthesis of different aryl derivatives (scheme 2.1).



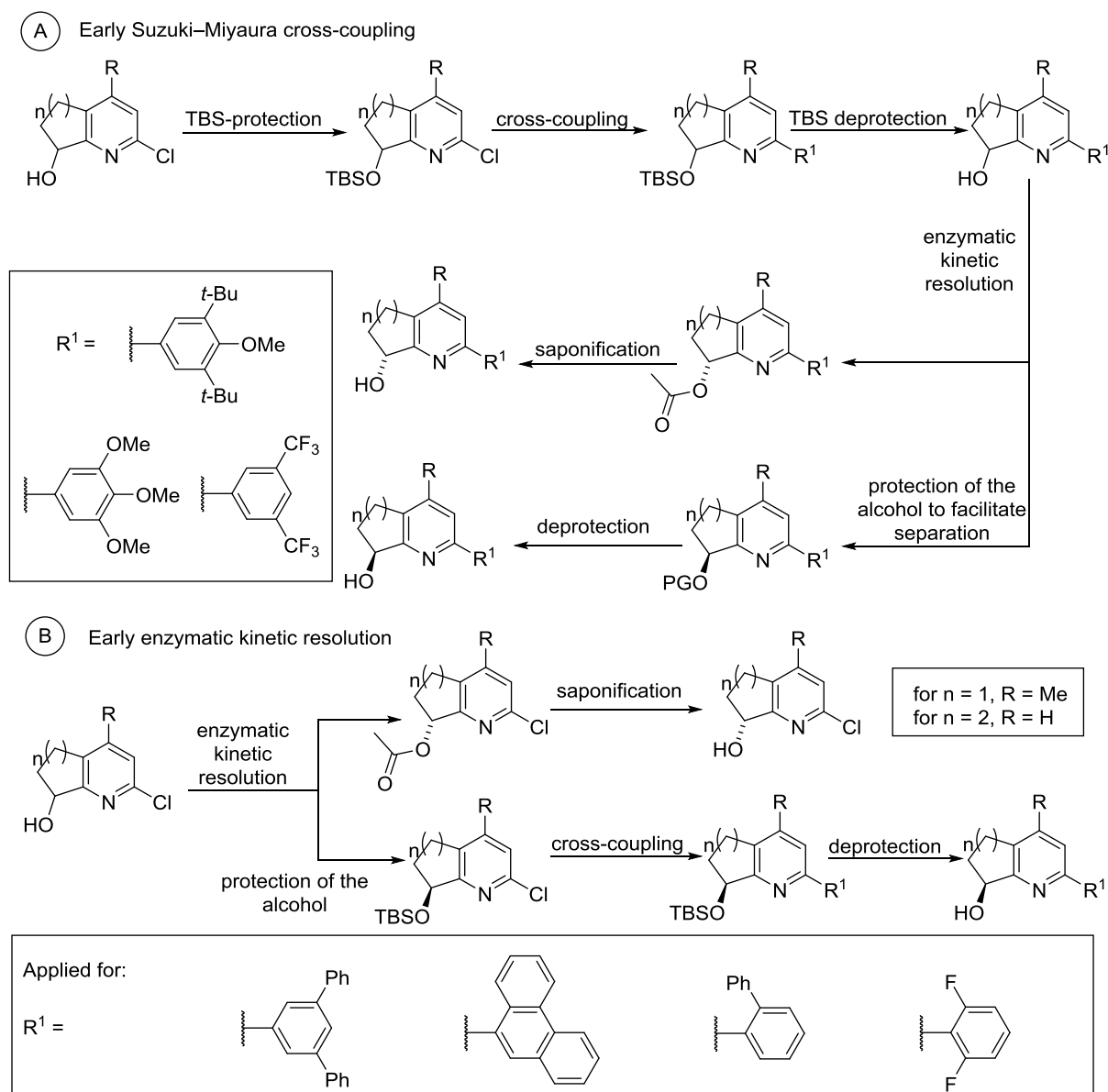
**Scheme 2.1:** Optimized synthesis of the pyridine-based iridium complexes. **a:** Mannich reaction; **b:** substitution; **c:** condensation; **d:** *N*-oxide formation; **e:** Boekelheide reaction followed by saponification **f:** enzymatic kinetic resolution **g:** phosphinite formation followed by complexation.

Therefore, an alternative route was elaborated with the goal to establish a flexible synthesis allowing for the derivatization of the ligand at a late stage of the synthesis. Shortly after the initial publication on the pyridine complexes bearing a phenyl substituent, Zhou and co-workers reported a route to nearly the same complexes that utilized a Suzuki–Miyaura cross-coupling to introduce the aromatic group on 2-chloropyridines at a late stage of the ligand synthesis.<sup>[56]</sup> Hence, the synthesis to the 2-chloro pyridyl alcohols **2.32** and **2.33** was achieved based on literature known procedures in overall 5% yield for 2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (**2.32**) and 11% yield for 2-chloro-5,6,7,8-tetrahydroquinolin-8-ol (**2.33**) (for details see experimental part).<sup>[57]</sup> As key step of the synthesis, the functionalization in the benzylic position was achieved by a Boekelheide rearrangement,<sup>[58]</sup> followed by saponification (scheme 2.2). These steps could be adopted from the original synthetic sequence.



**Scheme 2.2:** Retrosynthesis of the racemic 2-chloro pyridyl alcohols **2.32** and **2.33**.

With the racemic 2-chloropyridyl alcohols **2.32** and **2.33** in hand two different strategies were envisioned. The first using an early Suzuki cross coupling followed by enzymatic kinetic resolution of the different derivatives of the racemic pyridyl alcohols (scheme 2.3, A), whereas the second employs a enzymatic kinetic resolution on the stage of the racemic 2-chloro-pyridylalcohols, followed by TBS protection and Suzuki cross-coupling. The deprotection of the silyl ethers afforded the enantiopure pyridyl alcohols, which can be directly converted into the corresponding N,P ligand complexes (scheme 2.3, B). The first route is more labor intensive and will be not discussed in this chapter.<sup>[59]</sup> The second route proved to be significantly more efficient. This approach is two steps shorter and, even more importantly, the kinetic resolution representing the most laborious step of the whole synthesis can be performed before the derivatization step. The second route will be discussed in detail in this chapter. Data obtained previously, based on the 4,5-di-*tert*-butyl-4-methoxyphenyl, the 3,4,5 tri-methoxyphenyl and the 3,5-difluoromethylphenyl substituents, are provided to allow a complete discussion of this project.<sup>[59]</sup>

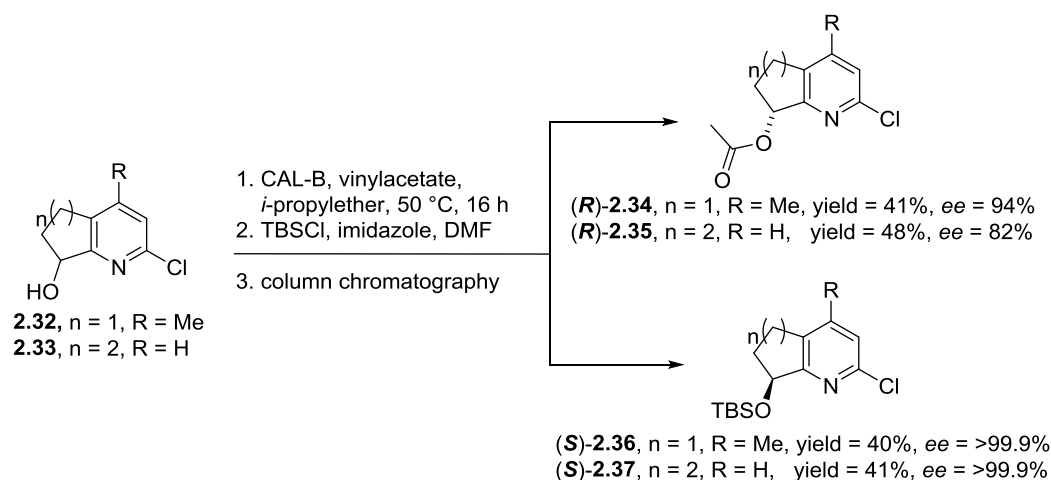


**Scheme 2.3:** Different strategies applied to access the enantiopure pyridyl alcohols.

The enzymatic kinetic resolution applied for the first synthesized pyridine-based complexes bearing a phenyl group at the 2-position of the pyridine moiety, was investigated Dr. Matthias Maywald,<sup>[60]</sup> based on the work of Uenishi and co-workers.<sup>[61]</sup> This method allowed for the synthesis of highly enantioenriched pyridyl alcohols in multigram scale. This protocol could be adopted for the resolution of racemic 2-chloro-substituted pyridyl alcohols **2.32** and **2.33** and achieved also in this case good selectivity (scheme 2.4). To achieve high enantiomeric excess for at least one enantiomer, the reaction progress was monitored by analytical HPLC and stopped after the complete consumption of the (*R*)-alcohols (*R*)-**2.32** or (*R*)-**2.33**. This approach provided the enantiomerically pure (*S*)-alcohols (*S*)-**2.32** or (*S*)-**2.33** in >99.9% *ee*. The mixture of the enantiopure alcohol and the enantioenriched acetates turned out to be

extremely difficult to separate. Therefore the free alcohol was TBS-protected, in order to facilitate the separation by column chromatography. The enantiomeric excess of the (*R*)-acetate (**(R)**-2.34 or (**(R)**-2.35 reached still useful values for recrystallizations.

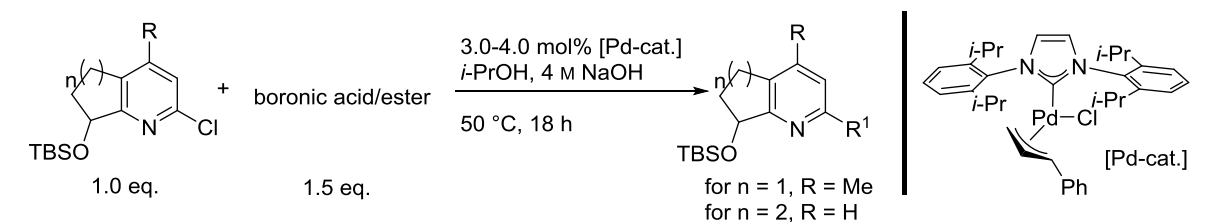
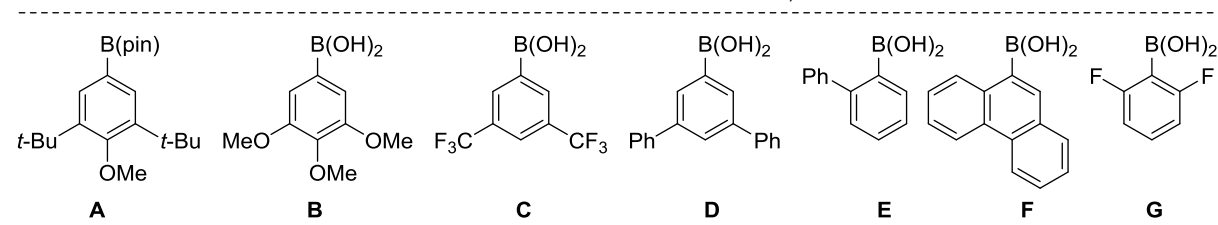
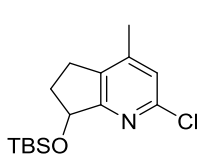
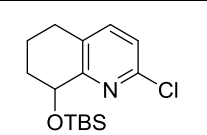
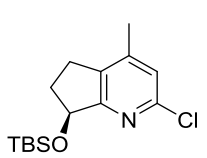
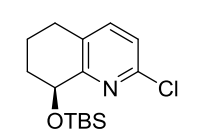
However, subjecting the free pyridyl alcohols to the Suzuki–Miyaura cross-coupling only traces of product were obtained, as reported by Dr. D. Woodmansee<sup>[54a]</sup> This might be explained by strong coordination of the pyridyl alcohols *via* a five-membered chelate ring to palladium. Hence, the TBS-protection is essential for the cross-coupling and did not represent an additional step needed only to allow the purification of the product (82% and 94% *ee*).



**Scheme 2.4:** Enzymatic kinetic resolution applied for the separation of the enantiomers.

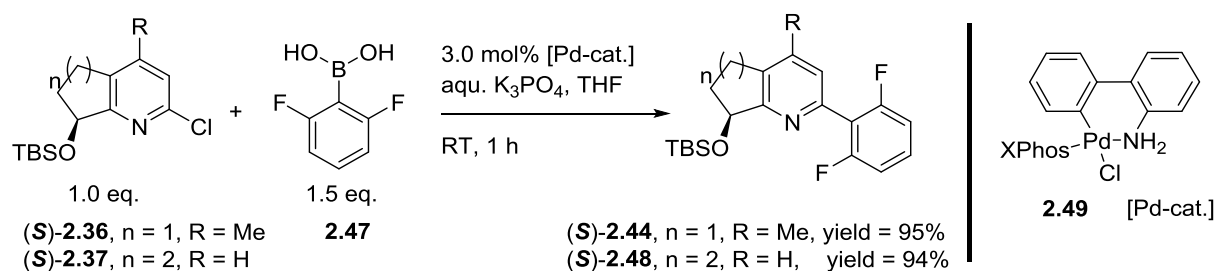
In the Suzuki–Miyaura cross-coupling excellent yields from 83% to 99% for a range of different aryl boronic esters were obtained (table 2.1). Only for the sterically demanding [1,1'-biphenyl]-2-ylboronic acid a moderate yield of 36% was obtained (entry 10). The introduction of the 2,6-difluorophenyl moiety failed under these reaction conditions and only dehydroborylated product was isolated.

**Table 2.1:** Preparation of the aryl derivatives by Suzuki–Miyaura cross-coupling.

				
				
Entry	Silyl ether	Boronic acid/ester	Product label	Yield [%]
1		<b>A</b>	<b>2.38</b>	88
2		<b>B</b>	<b>2.39</b>	95
3		<b>C</b>	<b>2.40</b>	86
4		<b>A</b>	<b>2.41</b>	97
5		<b>B</b>	<b>2.42</b>	91
6		<b>D</b>	<b>(S)-2.42</b>	60
7		<b>F</b>	<b>(S)-2.43</b>	99
8		<b>G</b>	<b>(S)-2.44</b>	--
9		<b>D</b>	<b>(S)-2.45</b>	83
10		<b>E</b>	<b>(S)-2.46</b>	36

Such dehydroborylations are frequently observed for electron deficient boronic acids and can be avoided by using palladium XPhos-based catalyst **2.49**, which was reported to be very efficient for the coupling of boronic acids such as **2.47**.<sup>[62]</sup> Applying this catalyst the cross-coupling was achieved with 94% and 95% yield (scheme 2.5).

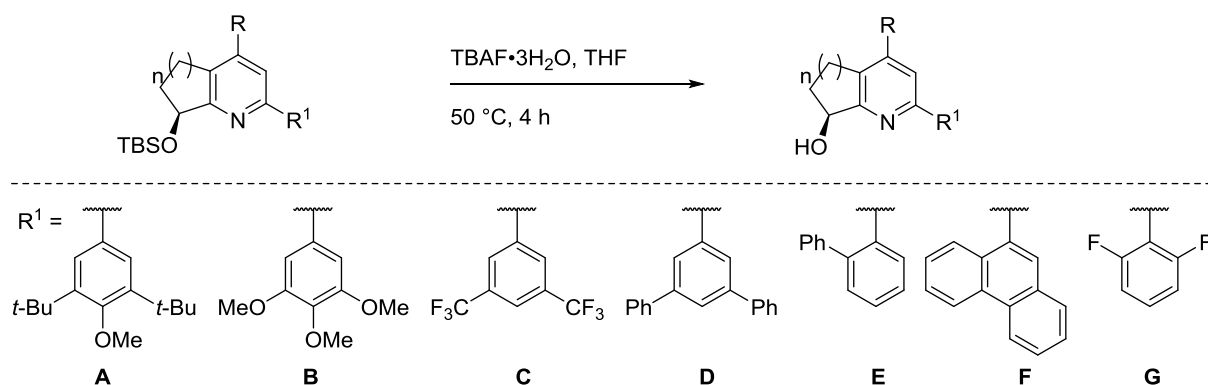




**Scheme 2.5:** Synthesis of the enantiopure pyridyl alcohols with a 2,6-difluoro substitution pattern on the aryl moiety.

After having installed the desired aryl moieties, the silyl ethers were cleaved to provide the pyridyl alcohols in good to excellent yields with no exception (table 2.2).

**Table 2.2:** Deprotection of the enantiopure silyl ether derivatives to afford the corresponding pyridyl alcohols.



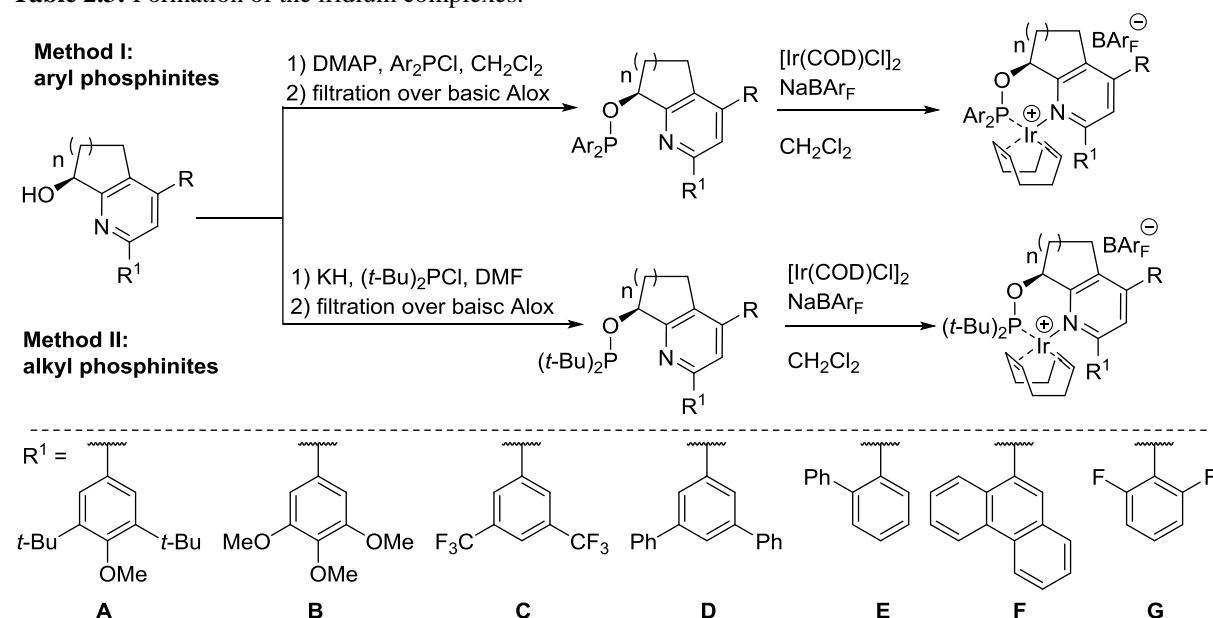
Entry	n	R	R <sup>1</sup>	Product label	Yield [%]
1	1	H	A	(S)-2.50	98
2	2	H	A	(S)-2.51	83
3	1	CH <sub>3</sub>	B	(S)-2.52	92
4	2	H	B	(S)-2.53	65
5	1	CH <sub>3</sub>	D	(S)-2.54	88
6	2	H	D	(S)-2.55	80
7	2	H	E	(S)-2.56	77
8	1	CH <sub>3</sub>	F	(S)-2.57	86
9	1	CH <sub>3</sub>	G	(S)-2.58	99
10	2	H	G	(S)-2.59	85

With the enantiopure pyridyl alcohols in hand, the phosphinite formation followed by subsequent complexation was the next and last step in the sequence (table 2.3). The

introduction of the aryl phosphinites was achieved using DMAP in combination with the corresponding diarylphosphinechloride. The obtained phosphinites were filtered over a plug of aluminum oxide and were directly converted in the presence of  $[\text{Ir}(\text{COD})\text{Cl}]_2$  and  $\text{NaBAR}_\text{F}$  to the desired iridium complexes.<sup>[54b]</sup> However, this protocol is not applicable for the synthesis of di-*tert*-butyl phosphinites, which were obtained from pyridyl alcohols in the presence of KH in DMF and di-*tert*-butyl phosphinechloride. Again, the obtained phosphinites were directly converted to the corresponding iridium-complexes in the presence of  $[\text{Ir}(\text{COD})\text{Cl}]_2$  and  $\text{NaBAR}_\text{F}$ .

The iridium complexes containing a diarylphosphinite residue were obtained in the majority of the cases in good yields. However, some pyridyl alcohols could not be converted into their corresponding iridium complexes. In the case of the aryl moieties B and C this might be explained by C–H activation which was observed to be a significant problem also for phosphine or amino phosphine-based catalysts of this type.<sup>[54, 59]</sup> Also the introduction of the sterically demanding di-*tert*-butyl phosphinites proved to be challenging in certain cases, indicated by the low yield obtained or irremovable impurities. However, twelve new catalysts were obtained, which were investigated in the hydrogenation of model substrates.

**Table 2.3:** Formation of the iridium complexes.

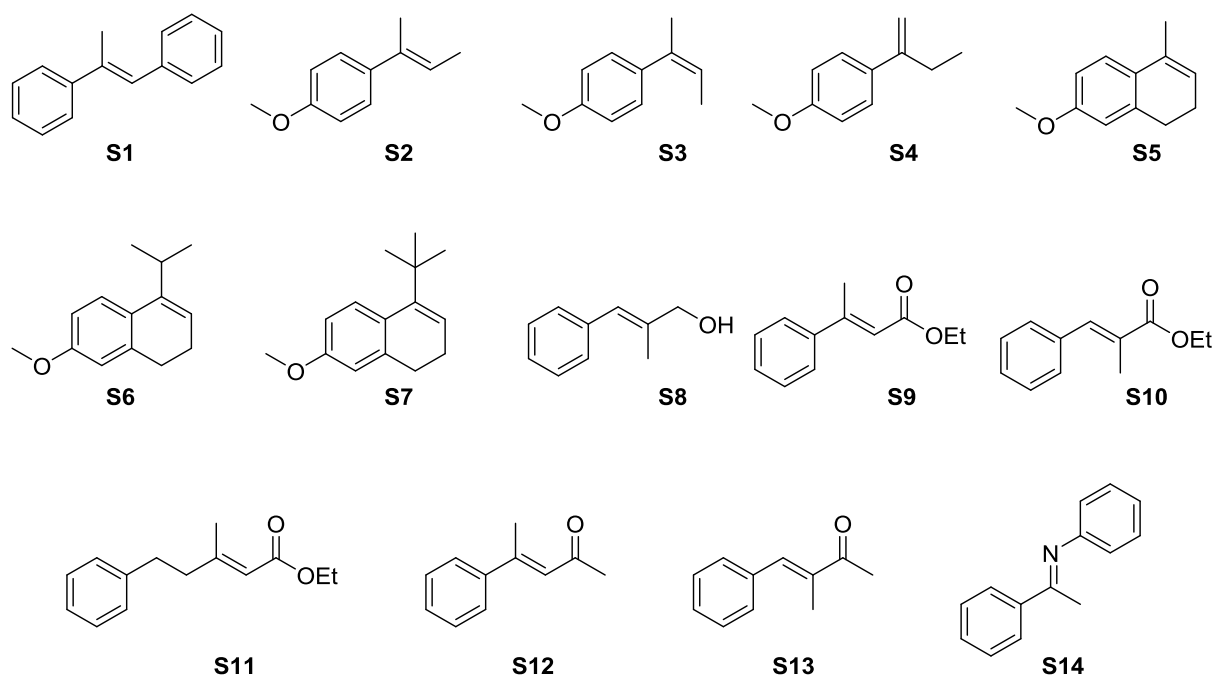


Entry	Method	n	R	R <sup>1</sup>	Yield [%]	Compound label	Remark
1	I, Ph	1	CH <sub>3</sub>	A	29	(S)-2.60	
2	I, <i>o</i> -Tol	1	CH <sub>3</sub>	A	73	(S)-2.61	

3	<b>I</b> , <i>o</i> -Tol	2		A	68	<b>(S)-2.62</b>	
4	<b>II</b> , <i>t</i> -Bu	1	CH <sub>3</sub>	A	51	<b>(R)-2.63</b>	
5	<b>I</b> , Ph	1	CH <sub>3</sub>	B	--		
6	<b>I</b> , <i>o</i> -Tol	1	CH <sub>3</sub>	B	--		
3	<b>I</b> , <i>o</i> -Tol	2		B	--		
7	<b>II</b> , <i>t</i> -Bu	1	CH <sub>3</sub>	B	--		
8	<b>I</b> , Ph	1	CH <sub>3</sub>	C	--		
9	<b>I</b> , <i>o</i> -Tol	1	CH <sub>3</sub>	C	--		
10	<b>II</b> , <i>t</i> -Bu	1	CH <sub>3</sub>	C	29%	<b>(S)-2.64</b>	5% impurity based on <sup>31</sup> P NMR
11	<b>I</b> , <i>o</i> -Tol	1	CH <sub>3</sub>	D	76	<b>(S)-2.65</b>	
12	<b>I</b> , <i>o</i> -Tol	2	H	D	72	<b>(S)-2.66</b>	
13	<b>II</b> , <i>t</i> -Bu	1	CH <sub>3</sub>	D	10		17% impurity based on <sup>31</sup> P NMR
14	<b>I</b> , <i>o</i> -Tol	2	H	E	65	<b>(S)-2.67</b>	
15	<b>II</b> , <i>t</i> -Bu	2	H	E	--		
16	<b>I</b> , <i>o</i> -Tol	1	CH <sub>3</sub>	F	49	<b>(S)-2.68</b>	
17	<b>II</b> , <i>t</i> -Bu	1	CH <sub>3</sub>	F	10	<b>(S)-2.69</b>	
18	<b>I</b> , <i>o</i> -Tol	1	CH <sub>3</sub>	G	--		Loss of BAr <sub>F</sub> (2 <sup>nd</sup> column on Alox)
19	<b>II</b> , <i>t</i> -Bu	2	H	G	56	<b>(S)-2.70</b>	
20	<b>I</b> , <i>o</i> -Tol	1	CH <sub>3</sub>	G	54	<b>(S)-2.71</b>	
21	<b>II</b> , <i>t</i> -Bu	2	H	G	40	<b>(S)-2.72</b>	

## 2.3 Hydrogenation Results

The new pyridyl phosphinite-based iridium complexes with sterically demanding aryl substituents were evaluated in the asymmetric hydrogenation of different model substrates. The set of these substrates includes different substituent patterns around the double bond, geometric isomers, a terminal double bond and double bonds embedded in a cyclic ring. Furthermore, different  $\alpha,\beta$ -unsaturated, functionalized olefins such as an allyl alcohol, different unsaturated carboxylic esters and ketones, plus a ketimine were investigated (figure 2.3). In addition, the obtained results were compared with the best results achieved by the use of the original iridium complexes with a phenyl group at the 2-position of the pyridine moiety. In a few cases the results obtained by Dr. D. Woodmansee in the course of his PhD work are reported to allow for a complete overview over the results obtained with these catalysts with a sterically more demanding aryl substituent.

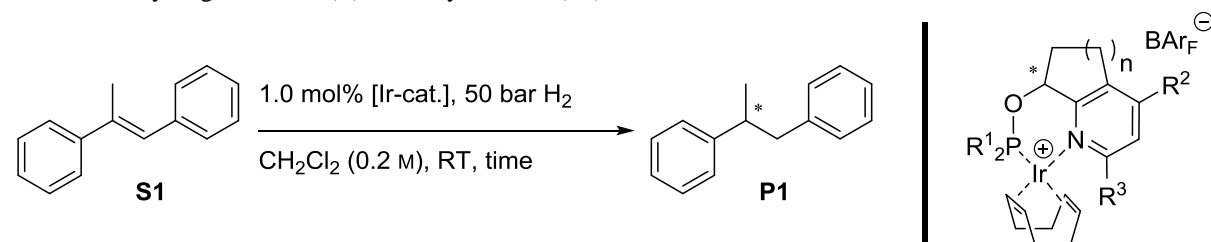


**Figure 2.3:** Different model substrates tested in the hydrogenation applying the newly synthesized catalysts.

(*E*)- $\alpha$ -Methylstilbene (**S1**) is one of the test substrates used to evaluate the performance of new catalysts and excellent enantioselectivity and full conversion have been previously achieved with many different catalyst classes. Although, it is rather simple to achieve good results for this substrate, its use allows for a first estimation of the performance of new catalysts. For the majority of the new complexes with sterically demanding aryl groups high

enantioselectivity and full conversion to propane-1,2-diylidibenzene (**P1**) were observed (table 2.4). Only for catalyst (*S*)-**2.62**, (*S*)-**2.71** and (*S*)-**2.67** incomplete conversion and for catalyst (*S*)-**2.67** moderate enantioselectivity were observed. All catalysts that showed incomplete conversion contain a six-membered aliphatic ring in the backbone. Also the parent complex with the phenyl substituent and the six-membered aliphatic ring showed reduced conversion for substrate **S1** and a maximum of 47% conversion was obtained.<sup>[52a]</sup> The catalysts with a sterically demanding aryl substituent and a six-membered ring in the backbone showed higher conversion when compared to the parent complex with a phenyl group at the 2-position of the pyridine moiety.

**Table 2.4:** Hydrogenation of (*E*)- $\alpha$ -methylstilbene (**S1**).

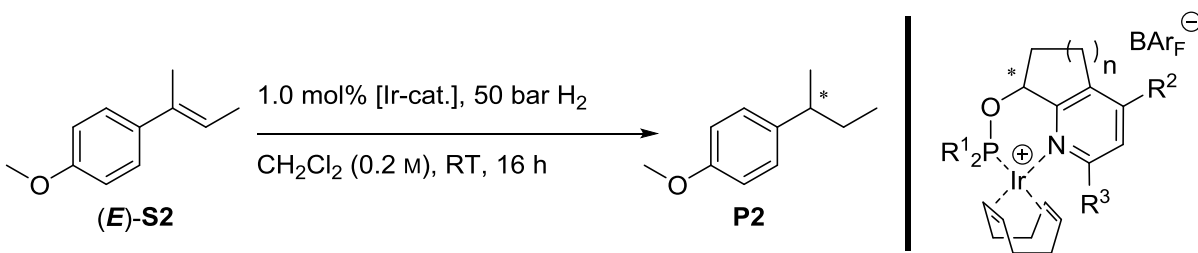
								
Entry <sup>[a]</sup>	No. Cat.	Time [h]	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.60</b>	3	1	Ph	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	99 ( <i>S</i> )
2	( <i>S</i> )- <b>2.61</b>	3	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	99 ( <i>S</i> )
3	( <i>R</i> )- <b>2.63</b>	3	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	94 ( <i>R</i> )
4	( <i>S</i> )- <b>2.62</b>	3	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	73	99 ( <i>S</i> )
5	( <i>S</i> )- <b>2.65</b>	15	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	>99	99 ( <i>S</i> )
6	( <i>S</i> )- <b>2.66</b>	15	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	>99	98 ( <i>S</i> )
7	( <i>S</i> )- <b>2.68</b>	15	1	<i>o</i> -Tol	CH <sub>3</sub>	phenanthren-9-yl	>99	>99 ( <i>S</i> )
8	( <i>S</i> )- <b>2.69</b>	15	1	<i>t</i> -Bu	CH <sub>3</sub>	phenanthren-9-yl	>99	96 ( <i>S</i> )
9	( <i>S</i> )- <b>2.70</b>	15	1	<i>t</i> -Bu	CH <sub>3</sub>	2,6-difluorophenyl	>99	99 ( <i>S</i> )
10	( <i>S</i> )- <b>2.71</b>	16	2	<i>o</i> -Tol	H	2,6-difluorophenyl	99	99 ( <i>S</i> )

11	( <i>S</i> )- <b>2.72</b>	16	2	<i>t</i> -Bu	H	2,6-difluorophenyl	>99	99 ( <i>S</i> )
12	( <i>S</i> )- <b>2.67</b>	15	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	21	76 ( <i>S</i> )
13 <sup>[52a]</sup>	( <i>S</i> )- <b>2.1</b>	2	1	<i>t</i> -Bu	H	Ph	>99	>99 ( <i>S</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by HPLC analysis on a chiral stationary phase.

Again, almost all catalysts showed high activity and selectivity in the hydrogenation of (*E*)-1-(but-2-en-2-yl)-4-methoxybenzene ((*E*)-**S2**) (table 2.5). With the exception of catalyst (*S*)-**2.67**, the enantiomeric excess was in the range between 92% and 97% (entries 1-8). Catalyst (*R*)-**2.63** reached with 97% the highest enantiomeric excess (entry 1). However, this value was lower compared to complex (*S*)-**2.1** bearing a phenyl group which reached up to >99% *ee* (entry 10).

**Table 2.5:** Hydrogenation of (*E*)-1-(but-2-en-2-yl)-4-methoxybenzene ((*E*)-**S2**).

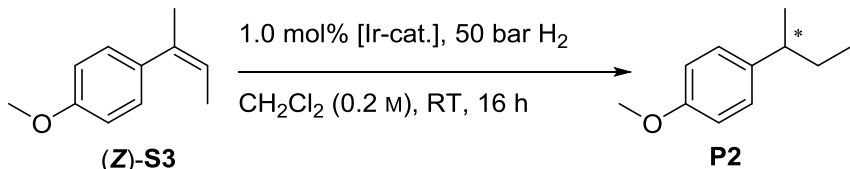
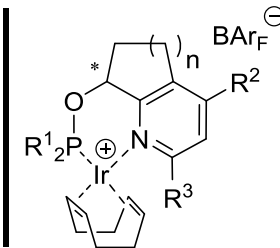
							
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1	( <i>R</i> )- <b>2.63</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	97 ( <i>R</i> )
2	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	95 ( <i>S</i> )
3	( <i>S</i> )- <b>2.65</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	>99	96 ( <i>S</i> )
4	( <i>S</i> )- <b>2.66</b>	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	>99	95 ( <i>S</i> )
5	( <i>S</i> )- <b>2.68</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	phenanthren-9-yl	>99	96 ( <i>S</i> )
6	( <i>S</i> )- <b>2.69</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	phenanthren-9-yl	>99	95 ( <i>S</i> )

7	(S)-2.71	2	<i>o</i> -Tol	H	2,6-difluorophenyl	>99	92 ( <i>S</i> )
8	(S)-2.72	2	<i>t</i> -Bu	H	2,6-difluorophenyl	>99	95 ( <i>S</i> )
9	(S)-2.67	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	>99	72 ( <i>S</i> )
10	(S)-2.1	1	<i>t</i> -Bu	H	Ph	>99	>99 ( <i>S</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase.

The hydrogenation of (*Z*)-1-(but-2-en-2-yl)-4-methoxybenzene ((*Z*)-**S3**), the first substrate with the double bond in (*Z*)-geometry, resulted almost exclusively in full conversion and high enantiomeric excess (table 2.6). Overall better results were obtained in comparison to substrate (*E*)-**S2**. The best result was obtained by the use of the phenanthren-9-yl-substituted catalyst (*S*)-**2.68** achieving 99% enantiomeric excess and full conversion (entry 6). This is even higher compared to the best result obtained employing the phenyl-substituted catalyst (*S*)-**2.73**. In this case 98% *ee* and full conversion were observed.

**Table 2.6:** Hydrogenation of (*Z*)-1-(but-2-en-2-yl)-4-methoxybenzene ((*Z*)-**S3**).

 <p>(Z)-S3</p> <p>1.0 mol% [Ir-cat.], 50 bar H<sub>2</sub></p> <p>CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), RT, 16 h</p> <p>P2</p>							
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	(S)-2.61	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	97 ( <i>R</i> )
2	(R)-2.63	1	<i>t</i> -Bu	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	96 ( <i>S</i> )
3	(S)-2.62	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	97 ( <i>R</i> )
4	(S)-2.65	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	>99	96 ( <i>R</i> )

5	(S)- <b>2.66</b>	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	>99	96 ( <i>R</i> )
6	(S)- <b>2.68</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	phenanthren-9-yl	>99	99 ( <i>R</i> )
7	(S)- <b>2.69</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	phenanthren-9-yl	>99	98 ( <i>R</i> )
8	(S)- <b>2.71</b>	2	<i>o</i> -Tol	H	2,6-difluorophenyl	>99	97 ( <i>R</i> )
9	(S)- <b>2.72</b>	2	<i>t</i> -Bu	H	2,6-difluorophenyl	>99	96 ( <i>R</i> )
10	(S)- <b>2.67</b>	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	76	80 ( <i>R</i> )
11 <sup>[52a]</sup>	(S)- <b>2.73</b>	1	<i>o</i> -Tol	H	Ph	>99	98 ( <i>S</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase.

The hydrogenation of 1-(but-1-en-2-yl)-4-methoxybenzene (**S4**) resulted in the formation of the identical product **P2** as the hydrogenation of (*E*)- and (*Z*)-1-(but-2-en-2-yl)-4-methoxybenzene ((*E*)-**S2**) and (*Z*)-**S3**). Although for the two previously screened substrates excellent results were obtained, shifting the double bond to the terminal position resulted in a molecule exposing a completely different environment around the C=C bond to the catalysts. Also, normally 1 bar hydrogen pressure in combination with a shorter reaction time are sufficient to reach full conversion for terminal C=C bonds. In addition higher enantioselectivities were achieved by the use of 1 bar H<sub>2</sub> pressure.<sup>[29a]</sup>

With regard to catalyst (S)-**2.67**, all catalysts from this series achieved full conversion in the hydrogenation of substrate **S4** (table 2.7). Moderate to good enantiomeric excesses were observed for this olefin. The best *ee* with 82% is similar to the 80% *ee* obtained with the parent complex (entry 7 vs. entry 12)



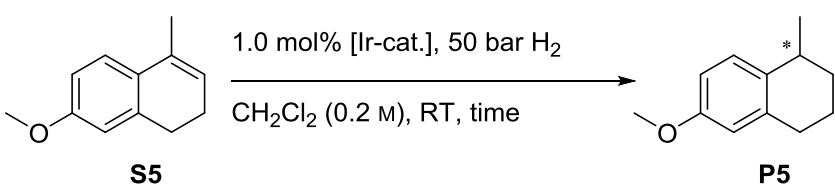
**Table 2.7:** Hydrogenation of 1-(but-1-en-2-yl)-4-methoxybenzene (**S4**).

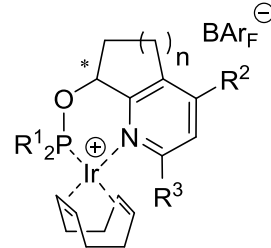
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.60</b>	1	Ph	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	66 ( <i>R</i> )
2	( <i>S</i> )- <b>2.61</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	76 ( <i>R</i> )
3	( <i>R</i> )- <b>2.63</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	72 ( <i>R</i> )
4	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	70 ( <i>R</i> )
5	( <i>S</i> )- <b>2.65</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	>99	34 ( <i>R</i> )
6	( <i>S</i> )- <b>2.66</b>	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	>99	80 ( <i>R</i> )
7	( <i>S</i> )- <b>2.68</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	phenanthren-9-yl	>99	82 ( <i>R</i> )
8	( <i>S</i> )- <b>2.69</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	phenanthren-9-yl	>99	17 ( <i>R</i> )
9	( <i>S</i> )- <b>2.70</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	2,6-difluorophenyl	>99	26 ( <i>R</i> )
10	( <i>S</i> )- <b>2.71</b>	2	<i>o</i> -Tol	H	2,6-difluorophenyl	>99	32 ( <i>R</i> )
11	( <i>S</i> )- <b>2.67</b>	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	85	63 ( <i>R</i> )
12 <sup>[52a]</sup> , <sup>[d]</sup>	( <i>S</i> )- <b>2.73</b>	1	<i>o</i> -Tol	H	Ph	>99	80 ( <i>R</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase; [d] 30 min reaction time.

Hydrogenation of 7-methoxy-4-methyl-1,2-dihydronaphthalene (**S5**) resulted in general in high enantioselectivities in combination with full conversion (table 2.8). Catalyst (*S*)-**2.66** containing a [1,1':3',1''-terphenyl]-5'-yl group on the aryl moiety reached even 99% enantiomeric excess and complete conversion (entry 6). These values were significantly higher when compared to the best result of the parent complex for which 92% *ee* was observed (entry 13).

**Table 2.8:** Hydrogenation of 7-methoxy-4-methyl-1,2-dihydronaphthalene (**S5**).





Entry <sup>[a]</sup>	No. Cat.	Time [h]	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.60</b>	3	1	Ph	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	97 ( <i>R</i> )
2	( <i>S</i> )- <b>2.61</b>	3	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	97 ( <i>R</i> )
3	( <i>R</i> )- <b>2.63</b>	3	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	99	94 ( <i>S</i> )
4	( <i>S</i> )- <b>2.62</b>	3	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	98 ( <i>R</i> )
5	( <i>S</i> )- <b>2.65</b>	15	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	96	99 ( <i>R</i> )
6	( <i>S</i> )- <b>2.66</b>	15	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	>99	99 ( <i>R</i> )
7	( <i>S</i> )- <b>2.68</b>	15	1	<i>o</i> -Tol	CH <sub>3</sub>	phenanthren-9-yl	>99	98 ( <i>R</i> )
8	( <i>S</i> )- <b>2.69</b>	15	1	<i>t</i> -Bu	CH <sub>3</sub>	phenanthren-9-yl	>99	97 ( <i>R</i> )
9	( <i>S</i> )- <b>2.70</b>	15	1	<i>t</i> -Bu	CH <sub>3</sub>	2,6-difluorophenyl	>99	88 ( <i>R</i> )
10	( <i>S</i> )- <b>2.71</b>	16	2	<i>o</i> -Tol	H	2,6-difluorophenyl	98	98 ( <i>R</i> )
11	( <i>S</i> )- <b>2.72</b>	16	2	<i>t</i> -Bu	H	2,6-difluorophenyl	>99	97 ( <i>R</i> )

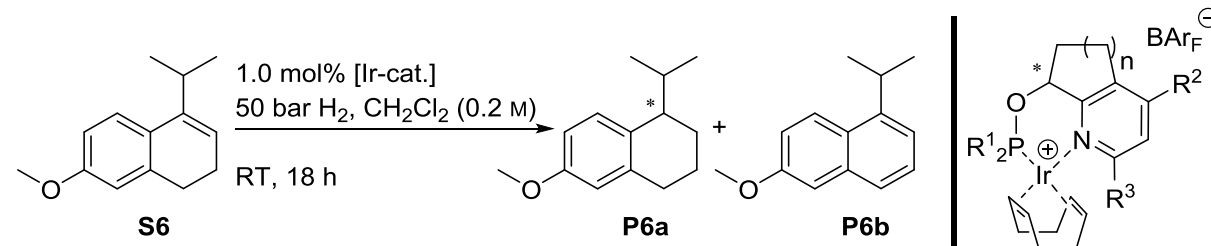
12	( <i>S</i> )- <b>2.67</b>	15	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	87	73 ( <i>R</i> )
13 <sup>[52a]</sup>	( <i>S</i> )- <b>2.1</b>	2	1	<i>t</i> -Bu	H	Ph	>99	92 ( <i>R</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by HPLC analysis on a chiral stationary phase.

With these promising results in hand, different cyclic olefins were tested as substrates in the hydrogenation with this newly synthesized catalyst. Replacement of the methyl substituent with an iso-propyl group resulted in a more challenging compound to reduce (table 2.9). In general incomplete conversion and the formation of up to 21% of the corresponding naphthalene **P6b** was observed. However, catalyst (*S*)-**2.72**, containing the 2,6-difluorophenyl substituent and the di-*tert*-butylphosphinite, showed with 98% *ee*, full conversion and no formation of the naphthalene **P6b**, excellent results (entry 5).

Anthracen-9-yl-substituted catalyst (*S*)-**2.74** afforded product **P6a** with 96% *ee* and 84% conversion (entry 6). However, these values could be increased to 98% *ee* and 99% conversion after optimization of the reaction conditions (entry 7).<sup>[54a]</sup>

**Table 2.9:** Hydrogenation of 4-isopropyl-7-methoxy-1,2-dihydronaphthalene (**S6**).

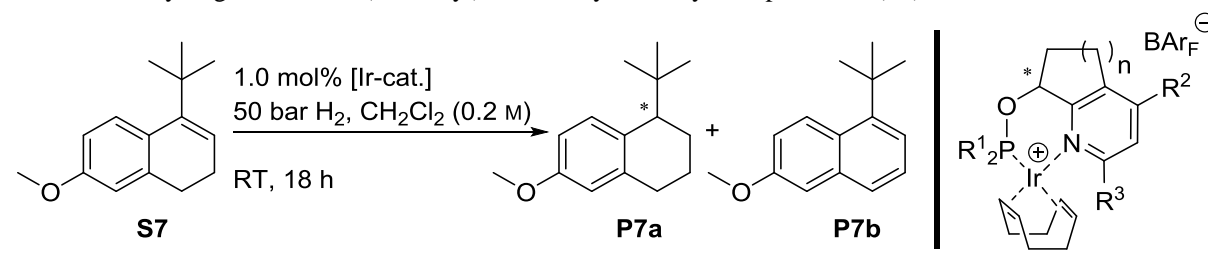
								
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>	P6b [%] <sup>[b]</sup>
1	( <i>S</i> )- <b>2.61</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	53	64 ( <i>R</i> )	7
2	( <i>R</i> )- <b>2.63</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	95 ( <i>S</i> )	1
3	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	14	28 ( <i>R</i> )	4
4	( <i>S</i> )- <b>2.66</b>	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	71	63 ( <i>R</i> )	21

5	( <i>S</i> )- <b>2.72</b>	2	<i>t</i> -Bu	H	2,6-difluorophenyl	>99	98 ( <i>R</i> )	0
6 <sup>[54a]</sup>	( <i>S</i> )- <b>2.74</b>	2	<i>o</i> -Tol	H	anthracen-9-yl	84	96 ( <i>R</i> )	2
7 <sup>[54a],[d]</sup>	( <i>S</i> )- <b>2.74</b>	2	<i>o</i> -Tol	H	anthracen-9-yl	99	98 ( <i>R</i> )	1

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase (**P6a+6b**); [c] Determined by HPLC analysis on a chiral stationary phase; [d] Reaction run at 2.0 mol% catalyst loading, 75 bar H<sub>2</sub> pressure for 3 h.

Next, the iso-propyl group was replaced by a *tert*-butyl group (table 2.10). Also in the hydrogenation of substrate **S7** by far the best result was obtained with catalyst (*S*)-**2.72** reaching an excellent 99% conversion, 97% *ee* and only 1% of the corresponding naphthalene **P7b** (entry 5).

**Table 2.10:** Hydrogenation of 4-(*tert*-butyl)-7-methoxy-1,2-dihydronaphthalene (**S7**).

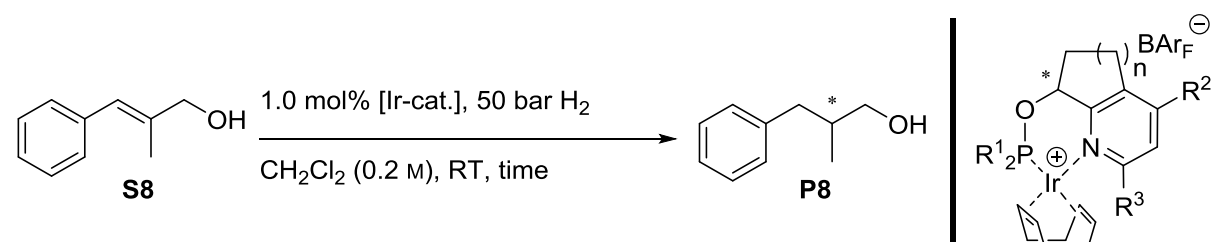
								
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>	<b>P7b</b> [%] <sup>[b]</sup>
1	( <i>S</i> )- <b>2.61</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	53	64 (–)	1
2	( <i>R</i> )- <b>2.63</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	96	47 (+)	1
3	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	52	33 (–)	1
4	( <i>S</i> )- <b>2.66</b>	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	71	59 (–)	5
5	( <i>S</i> )- <b>2.72</b>	2	<i>t</i> -Bu	H	2,6-difluorophenyl	99	97 (–) <sup>[d]</sup>	1
6 <sup>[54a],[e]</sup>	( <i>S</i> )- <b>2.74</b>	2	<i>o</i> -Tol	H	anthracen-9-yl	63	86	4

7<sup>[54a],[f]</sup> (*S*)-**2.74** 2 *o*-Tol H anthracen-9-yl >99 97 13

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase (**P7a+7b**); [c] Determined by HPLC analysis on a chiral stationary phase; [d]  $[\alpha]_D^{20} = -25.4$  ( $c = 0.81$ ,  $\text{CHCl}_3$ ); [e] Reaction run at 100 bar  $\text{H}_2$  pressure for 24 h; [f] Reaction run at 2.0 mol% catalyst loading, 100 bar  $\text{H}_2$  pressure, 1.0 M substrate concentration for 24 h.

The allylic alcohol **S8** is one of the more challenging substrates for Ir-catalyzed asymmetric hydrogenation and in the course of this process unpredictable side reactions such as oxidation, isomerization or polymerization can be observed.<sup>[20]</sup> Only three out of twelve catalysts achieved full conversion in the hydrogenation of this substrate (table 2.11, entry 3, 6, 8). For catalysts (*S*)-**2.71** and (*S*)-**2.72** with the 2,6-difluorophenyl aryl moiety even completed decomposition of the substrate was observed. The best results were observed for catalyst (*S*)-**2.65**, which reached full conversion and 95% *ee*. The enantiomeric excess is slightly lower compared to the best results obtained with catalyst (*S*)-**2.1** bearing the phenyl substituent and achieving 97% *ee* and full conversion (entry 13).

**Table 2.11:** Hydrogenation of (*E*)-2-methyl-3-phenylprop-2-en-1-ol (**S8**).

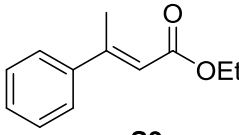
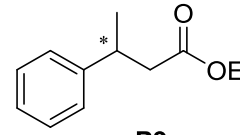
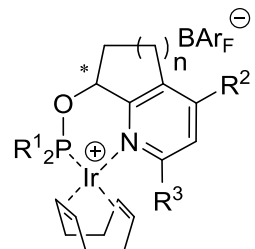
								
Entry <sup>[a]</sup>	No. Cat.	Time [h]	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.60</b>	3	1	Ph	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	70	92 ( <i>R</i> )
2	( <i>S</i> )- <b>2.61</b>	3	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	40	93 ( <i>R</i> )
3	( <i>S</i> )- <b>2.61</b>	5	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	93 ( <i>R</i> )
4 <sup>[d]</sup>	( <i>R</i> )- <b>2.63</b>	14	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	62	12 ( <i>S</i> )
5	( <i>S</i> )- <b>2.62</b>	16	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	34	86 ( <i>R</i> )
6	( <i>S</i> )- <b>2.65</b>	16	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	>99	95 ( <i>R</i> )

7	( <i>S</i> )- <b>2.66</b>	16	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	78	97 ( <i>R</i> )
8	( <i>S</i> )- <b>2.68</b>	16	1	<i>o</i> -Tol	CH <sub>3</sub>	phenanthren-9-yl	>99	93 ( <i>R</i> )
9	( <i>S</i> )- <b>2.69</b>	16	1	<i>t</i> -Bu	CH <sub>3</sub>	phenanthren-9-yl	24	67 ( <i>R</i> )
10 <sup>[e]</sup>	( <i>S</i> )- <b>2.71</b>	16	2	<i>o</i> -Tol	H	2,6-difluorophenyl	--	--
11 <sup>[e]</sup>	( <i>S</i> )- <b>2.72</b>	16	2	<i>t</i> -Bu	H	2,6-difluorophenyl	--	--
12	( <i>S</i> )- <b>2.67</b>	16	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	15	n.d.
13 <sup>[52a]</sup>	( <i>S</i> )- <b>2.1</b>	2	1	<i>t</i> -Bu	H	Ph	>99	97 ( <i>R</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase; [d] 15% unidentified byproduct observed; [e] Complete decomposition of the substrate was observed.

Investigating (*E*)- $\beta$ -methylcinnamic acid ethyl ester (**S9**) as substrate with these catalysts showed overall excellent enantioselectivities (table 2.12). All catalysts bearing the 2,6-difluorophenyl substituent reached 99% enantiomeric excess with full conversion (entries 8, 9 and 10). But also the phenyl-substituted complex (*S*)-**2.1** achieved with >99% *ee* and full conversion excellent results in the hydrogenation of this substrate (entry 13).

**Table 2.12:** Hydrogenation of (*E*)- $\beta$ -methylcinnamic acid ethyl ester (**S9**).

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p><b>S9</b></p> </div> <div style="text-align: center;"> <p>1.0 mol% [Ir-cat.] 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> (0.2 M) RT, time</p> </div> <div style="text-align: center;">  <p><b>P9</b></p> </div> <div style="border-left: 1px solid black; padding-left: 10px;">  </div> </div>								
Entry <sup>[a]</sup>	No. Cat.	Time [h]	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.60</b>	5	1	Ph	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	88	56 ( <i>S</i> )
2	( <i>S</i> )- <b>2.61</b>	5	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	96	92 ( <i>S</i> )
3	( <i>R</i> )- <b>2.63</b>	14	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	93 ( <i>R</i> )

4	( <i>S</i> )- <b>2.62</b>	5	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	8	71 ( <i>S</i> )
5	( <i>S</i> )- <b>2.65</b>	16	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	76	93 ( <i>S</i> )
6	( <i>S</i> )- <b>2.66</b>	16	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	77	97 ( <i>S</i> )
7	( <i>S</i> )- <b>2.68</b>	16	1	<i>o</i> -Tol	CH <sub>3</sub>	phenanthren-9-yl	>99	98 ( <i>S</i> )
8	( <i>S</i> )- <b>2.69</b>	16	1	<i>t</i> -Bu	CH <sub>3</sub>	phenanthren-9-yl	>99	>99 ( <i>S</i> )
9	( <i>S</i> )- <b>2.72</b>	16	1	<i>t</i> -Bu	CH <sub>3</sub>	2,6-difluorophenyl	>99	>99 ( <i>S</i> )
10	( <i>S</i> )- <b>2.71</b>	16	2	<i>o</i> -Tol	H	2,6-difluorophenyl	>99	99 ( <i>S</i> )
11	( <i>S</i> )- <b>2.72</b>	16	2	<i>t</i> -Bu	H	2,6-difluorophenyl	>99	99 ( <i>S</i> )
12	( <i>S</i> )- <b>2.67</b>	16	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	40	44 ( <i>S</i> )
13 <sup>[52a]</sup>	( <i>S</i> )- <b>2.1</b>	2	1	<i>t</i> -Bu	H	Ph	>99	>99 ( <i>S</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase.

The C=C bond of the  $\alpha,\beta$ -unsaturated ester **S10** was reduced with variable results. Catalyst (**R**)-**2.63** with the 3,5-di-*tert*-butyl-4-methoxyphenyl-substituted pyridine ring achieved 95% *ee* and full conversion (table 2.13, entry 3). This is significantly higher compared to the best result obtained with the parent complex reaching a maximum of 69% *ee* (entry 6). However, the overall best result obtained from this new catalyst class was obtained with the mesitylene-substituted catalyst (*S*)-**2.75** with 97% *ee* and full conversion (entry 7).<sup>[54a]</sup>

**Table 2.13:** Hydrogenation of (*E*)- $\beta$ -methylcinnamic acid ethyl ester (**S10**).

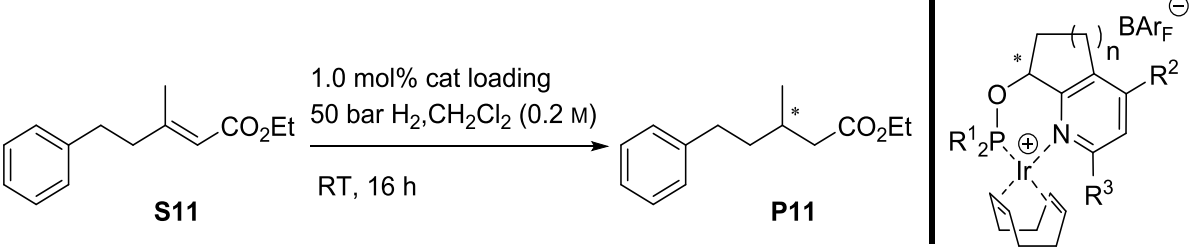
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.60</b>	1	Ph	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	71	29 ( <i>R</i> )
2	( <i>S</i> )- <b>2.61</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	98	8( <i>R</i> )
3	( <i>R</i> )- <b>2.63</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	95 ( <i>S</i> )
4	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	39	6 ( <i>R</i> )
5	( <i>S</i> )- <b>2.67</b>	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	5	n.d.
6 <sup>[52a]</sup>	( <i>S</i> )- <b>2.1</b>	1	<i>t</i> -Bu	H	Ph	>99	69 ( <i>R</i> )
7 <sup>[54a]</sup>	( <i>S</i> )- <b>2.75</b>	1	<i>t</i> -Bu	H	mesityl	>99	97 ( <i>R</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase.

In the hydrogenation of (*E*)-ethyl  $\beta$ -methyl-5-phenylpent-2-enoate (**S11**), these catalysts showed lower enantioselectivities compared to the other  $\alpha,\beta$ -unsaturated esters **S9** and **S10** (table 2.14). Catalyst (*S*)-**2.71** containing a 2,6-difluoro substituent achieved with 88% *ee* and full conversion the best results. This is slightly better compared to the parent complex (entry 9). However, the highest selectivity was observed with this catalyst class using the mesityl-substituted catalyst (*S*)-**2.75** with 94% *ee* while reaching full conversion (entry 10).<sup>[54a]</sup>



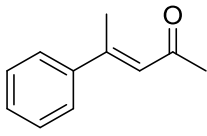
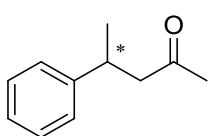
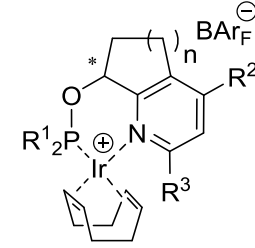
**Table 2.14:** Hydrogenation of (*E*)-ethyl β-methyl-5-phenylpent-2-enoate (**S11**).

							
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.60</b>	1	Ph	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	18 ( <i>R</i> )
2	( <i>S</i> )- <b>2.61</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	20 ( <i>R</i> )
3	( <i>R</i> )- <b>2.63</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	40 ( <i>S</i> )
4	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	<i>rac</i>
5	( <i>S</i> )- <b>2.65</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	75	84 ( <i>R</i> )
6	( <i>S</i> )- <b>2.71</b>	2	<i>o</i> -Tol	H	2,6-difluorophenyl	>99	88 ( <i>R</i> )
7	( <i>S</i> )- <b>2.72</b>	2	<i>t</i> -Bu	H	2,6-difluorophenyl	>99	65 ( <i>R</i> )
8	( <i>S</i> )- <b>2.67</b>	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	25	37 ( <i>R</i> )
9 <sup>[53a]</sup>	( <i>S</i> )- <b>2.1</b>	1	<i>t</i> -Bu	H	Ph	>99	86 ( <i>R</i> )
10 <sup>[53a]</sup>	( <i>S</i> )- <b>2.75</b>	1	<i>t</i> -Bu	H	mesityl	>99	94 ( <i>R</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase.

(*E*)-4-Phenylpent-3-en-2-one (**S12**) was not investigated as substrate with this catalyst class so far. Only the catalyst (*S*)-**2.71** bearing the 2,6-difluorophenyl group reached full conversion but only moderate enantiomeric excess was observed (table 2.15). Switching from the di-*o*-tolyl phosphinite to the di-*tert*-butyl phosphinite resulted in 89% enantiomeric excess but conversion remained at 50%.

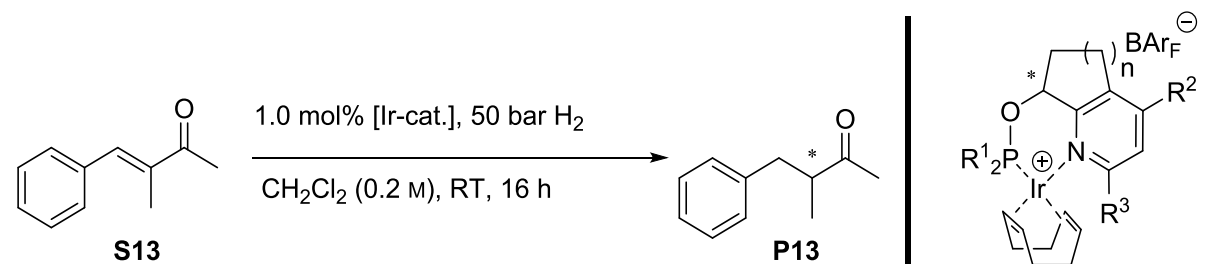
**Table 2.15:** Hydrogenation of (*E*)-4-phenylpent-3-en-2-one (**S12**).

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p><b>S12</b></p> </div> <div style="text-align: center;"> <math>\xrightarrow[\text{CH}_2\text{Cl}_2 \text{ (0.2 M), RT, 16 h}]{1.0 \text{ mol\% [Ir-cat.], 50 bar H}_2}</math> </div> <div style="text-align: center;">  <p><b>P12</b></p> </div> </div> <div style="text-align: right; margin-top: 10px;">  </div>							
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.61</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	35	91 ( <i>S</i> )
2	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	3	n.d.
3	( <i>S</i> )- <b>2.65</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	6	73 ( <i>S</i> )
4	( <i>S</i> )- <b>2.66</b>	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	32	87 ( <i>S</i> )
5	( <i>S</i> )- <b>2.71</b>	2	<i>o</i> -Tol	H	2,6-difluorophenyl	>99	73 ( <i>S</i> )
6	( <i>S</i> )- <b>2.72</b>	2	<i>t</i> -Bu	H	2,6-difluorophenyl	50	89 ( <i>S</i> )
7	( <i>S</i> )- <b>2.67</b>	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	3	n.d.

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase.

Also (*E*)-3-methyl-4-phenylbut-3-en-2-one (**S13**) was not investigated as substrate with this catalyst class so far. In general high enantiomeric excesses between 96% and >99% in combination with full conversions were observed (table 2.16). Three catalysts of this series even achieved >99% *ee* (entries 2, 3 and 4). Therefore, the obtained data demonstrate the high efficiency of this catalyst class to hydrogenate the  $\alpha,\beta$ -unsaturated ketone **S13**. In contrast to the  $\beta,\beta$ -disubstituted  $\alpha,\beta$ -unsaturated ketone **S12**, both conversion and enantiomeric excess were significantly higher.

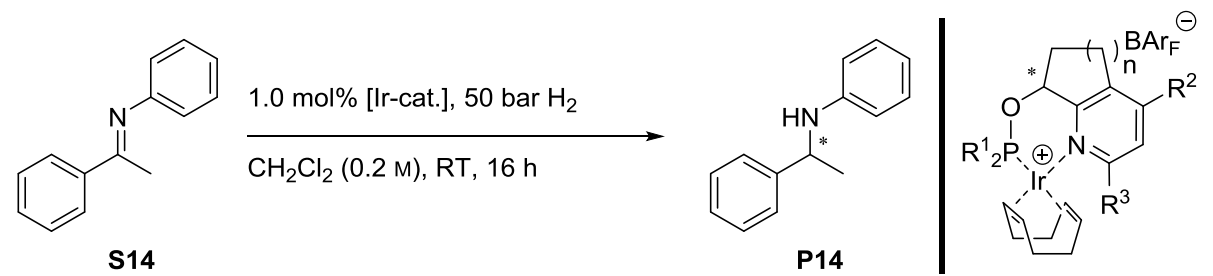
**Table 2.16:** Hydrogenation of (*E*)-3-methyl-4-phenylbut-3-en-2-one (**S13**).

							
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.1</b>	1	<i>t</i> -Bu	H	Ph	>99	99 (–)
2	( <i>S</i> )- <b>2.61</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	>99 (–)
3	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	>99	>99 (–)
4	( <i>S</i> )- <b>2.65</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	[1,1':3',1''-terphenyl]-5'-yl	>99	99 (–)
5	( <i>S</i> )- <b>2.66</b>	2	<i>o</i> -Tol	H	[1,1':3',1''-terphenyl]-5'-yl	>99	>99 (–)
6	( <i>S</i> )- <b>2.71</b>	2	<i>o</i> -Tol	H	2,6-difluorophenyl	>99	96 (–)
7	( <i>S</i> )- <b>2.72</b>	2	<i>t</i> -Bu	H	2,6-difluorophenyl	>99	98 (–)
8	( <i>S</i> )- <b>2.67</b>	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	13	98 (–)

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase.

Imines represent another substrate class that can be reduced with high enantioselectivity with iridium N,P ligand complexes. (*E*)-*N*,1-Diphenylethan-1-imine (**S14**) showed low selectivities and incomplete conversions were reduced with all catalyst of this series (table 2.17). Recently our research group demonstrated that a C–H activation of the substrate plays a crucial role in the activity obtained for this substrate class.<sup>[63]</sup> This might explain the lower reactivity for the sterically more encumbered complexes, because these catalysts should have a much lower affinity to form such Ir(III)-species.

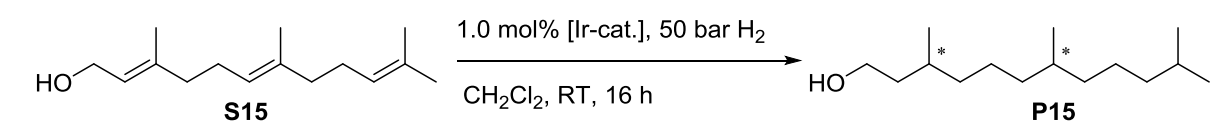
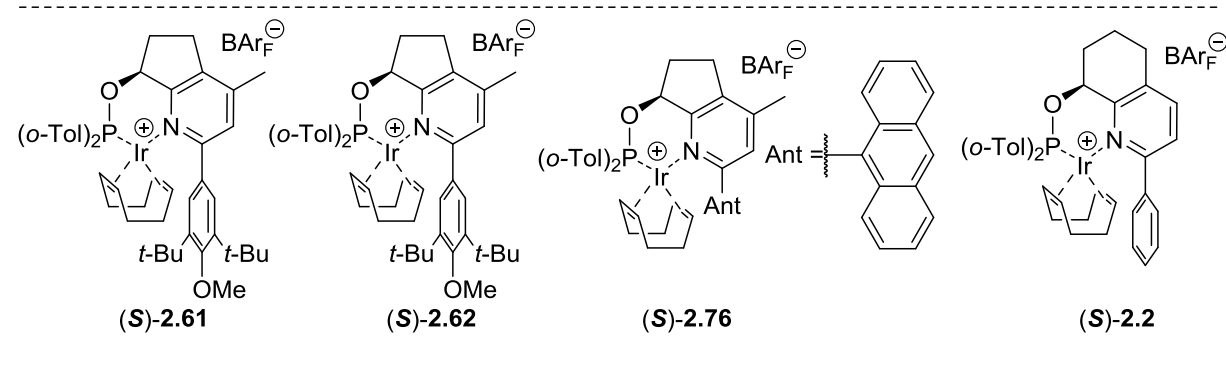
**Table 2.17:** Hydrogenation of (*E*)-*N*,1-diphenylethan-1-imine (**S14**).

							
Entry <sup>[a]</sup>	No. Cat.	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	( <i>S</i> )- <b>2.60</b>	1	Ph	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	24	14 ( <i>S</i> )
2	( <i>S</i> )- <b>2.61</b>	1	<i>o</i> -Tol	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	14	31 ( <i>S</i> )
3	( <i>R</i> )- <b>2.63</b>	1	<i>t</i> -Bu	CH <sub>3</sub>	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	8	31 ( <i>R</i> )
4	( <i>S</i> )- <b>2.62</b>	2	<i>o</i> -Tol	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	13	29 ( <i>S</i> )
5	( <i>S</i> )- <b>2.71</b>	2	<i>o</i> -Tol	H	2,6-difluorophenyl	14	28 ( <i>S</i> )
6	( <i>S</i> )- <b>2.72</b>	2	<i>t</i> -Bu	H	2,6-difluorophenyl	40	<i>rac</i>
7	( <i>S</i> )- <b>2.67</b>	2	<i>o</i> -Tol	H	[1,1'-biphenyl]-2-yl	39	<i>rac</i>
8 <sup>[52a]</sup>	( <i>S</i> )- <b>2.2</b>	1	<i>o</i> -Tol	H	Ph	>99	82 ( <i>S</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by GC analysis on a chiral stationary phase.

As last substrate (3*E*,7*E*)-farnesol (**S15**) was investigated in combination with this catalyst class (table 2.18). (3*E*,7*E*)-Farnesol (**S15**) is a mimic of the vitamin E side chain and was previously successfully hydrogenated employing the catalyst with a phenyl group at the 2-position of the pyridine ring. In this case 92.2% of the main stereoisomer was obtained (entry 4).<sup>[53b]</sup> This result was further improved with the mesityl-substituted catalyst (*S*)-**2.76**, which afforded 95.1% of the major diastereoisomer.

**Table 2.18:** Hydrogenation of (3*E*,7*E*)-farnesol (**S15**).

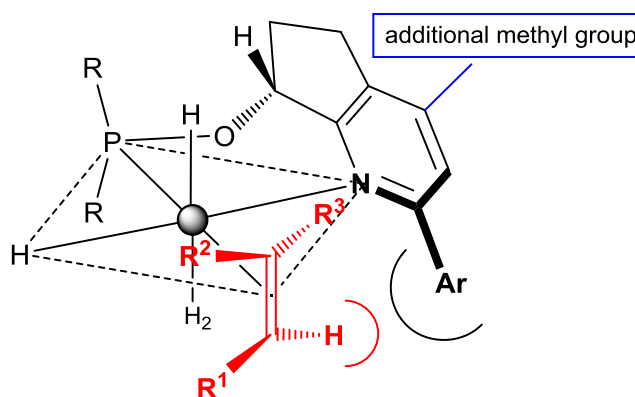
							
							
Entry <sup>[a]</sup>	Cat.	(3 <i>S</i> ,7 <i>R</i> ) [%] <sup>[b]</sup>	(3 <i>R</i> ,7 <i>R</i> ) [%] <sup>[b]</sup>	(3 <i>R</i> ,7 <i>S</i> ) [%] <sup>[b]</sup>	(3 <i>S</i> ,7 <i>S</i> ) [%] <sup>[b]</sup>	<i>ee</i> [%] (3 <i>R</i> ,7 <i>R</i> )	<i>de</i> [%]
1	( <i>S</i> )- <b>2.61</b>	26.2	62.5	7.3	3.3	90	32
2	( <i>S</i> )- <b>2.62</b>	22.1	69.8	7.3	1.4	96	42
3	( <i>S</i> )- <b>2.76</b>	4.1	95.1	0.8	0.1	>99	90
4 <sup>[53b]</sup>	( <i>S</i> )- <b>2.2</b>	6.4	92.2	1.3	0.3	>99	85

[a] Full conversion was obtained for all entries; [b] Determined by GC on a chiral stationary phase.<sup>[53b]</sup> Due to difficult separation the sum of all stereoisomers does not result in 100%.

## 2.4 Influence of the methyl group at the 4-position of the pyridine moiety

As already discussed, the newly developed catalyst with more sterically demanding aryl groups emerged as superior in the hydrogenation of certain model substrates. However, the catalysts with an aliphatic five-membered ring in the backbone of the ligand differ from earlier established pyridyl-phosphinite catalysts not only on the aryl position, but also with respect to the methyl group at the 4-position of the pyridine ring. The introduction of this methyl group was part of the modification of the original synthetic route, which reduced the sequence by one step and allowed for the synthesis of these ligands starting from extremely cheap starting materials (see scheme 2.2).

Based on the quadrant model used to predict the stereochemical outcome of iridium-catalyzed asymmetric hydrogenations developed by Andersson and co-workers, this additional methyl group points away from the chiral pocket formed by the ligand around the metal center (figure 2.4). Therefore, no significant influence on both reactivity and selectivity is expected. On the other hand, the methyl group could have a slight influence on the electron density of the pyridine ring and could potentially interact with the aliphatic backbone of the ligand, thus influencing its geometry and ultimately the enantioselectivity of the overall process.

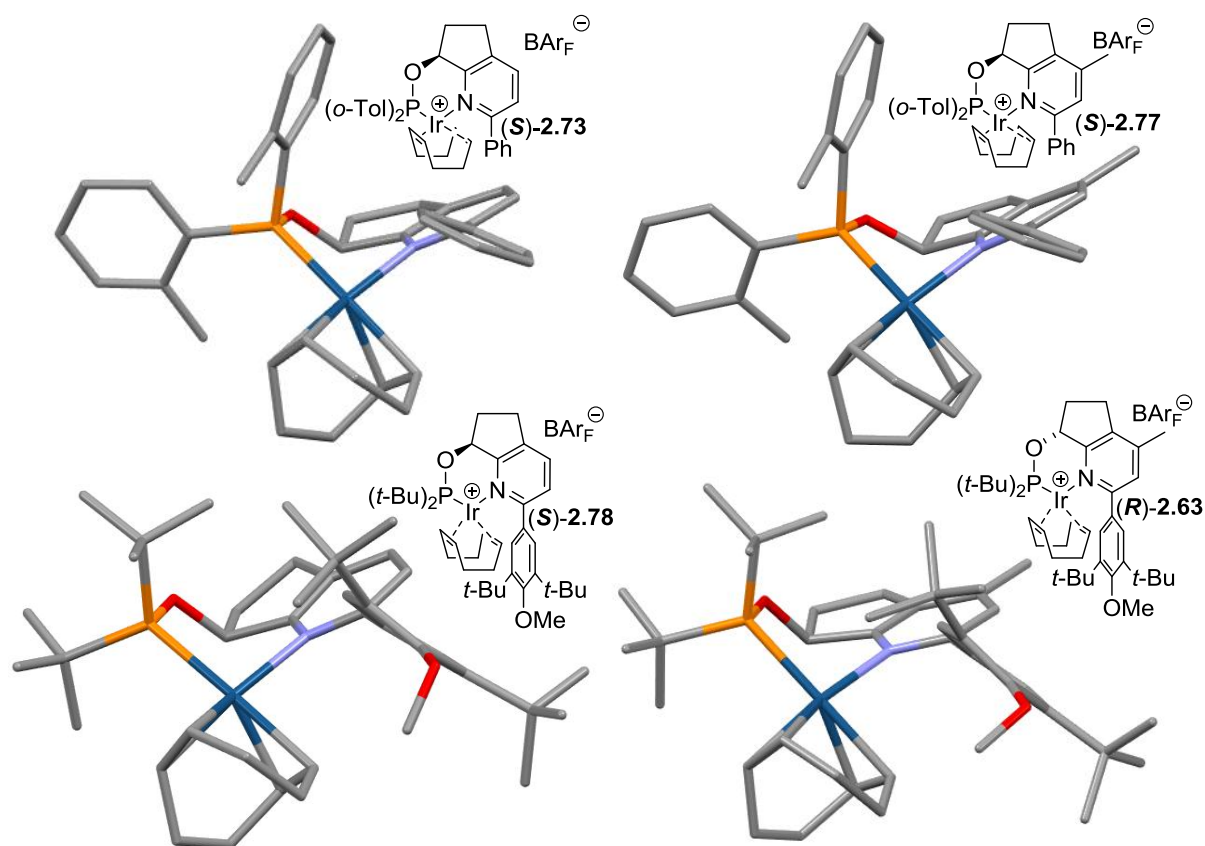


**Figure 2.4:** Andersson's model explaining the enantioselectivity-determining step with the additional methyl group pointing away from the chiral pocket formed by the ligand.

Therefore, catalysts of this ligand class, either bearing or lacking a methyl group at the 4-position of the pyridine moiety, were prepared according to the previously described methods to investigate the influence of this structural element.

### 2.4.1 Crystal structures of iridium N,P ligand complexes with and without a methyl group at the 4-position of the pyridine moiety

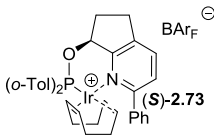
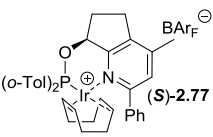
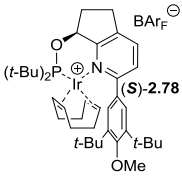
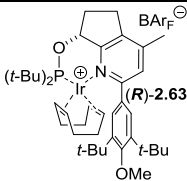
In the course of this project it was possible to grow crystals of complexes (*R*)-**2.73**, (*R*)-**2.77** and (*R*)-**2.63** that were suitable for X-ray analysis. Such analyses allowed for the comparison of the crystal structures of the complexes with and without a methyl group at the 4-position of the pyridine ring (figure 2.5). The crystal structure of complex (*S*)-**2.73** was kindly provided by Dr. Adnan Ganić.



**Figure 2.5:** Crystal structures of complexes (*S*)-**2.73**, (*S*)-**2.77** and (*S*)-**2.73**, (*R*)-**2.63** bearing an additional methyl group (right); counterions were omitted for clarity. The crystal structure of (*R*)-**2.63** is depicted as mirror image.

By comparing the bond lengths, the angles and the orientation of the complex with and without the methyl group on the pyridine ring, almost identical values were obtained. Only the torsion angle between the pyridine plane and the plane of the aryl moiety for catalyst (*S*)-**2.73** and (*R*)-**2.63** showed a notable discrepancy of 9°. However, the crystal structures depicted in figure 2.5 represent only the precatalyst and on their basis definite conclusions on the orientation of each group in the enantioselectivity-determining step of the hydrogenation would be just speculative.

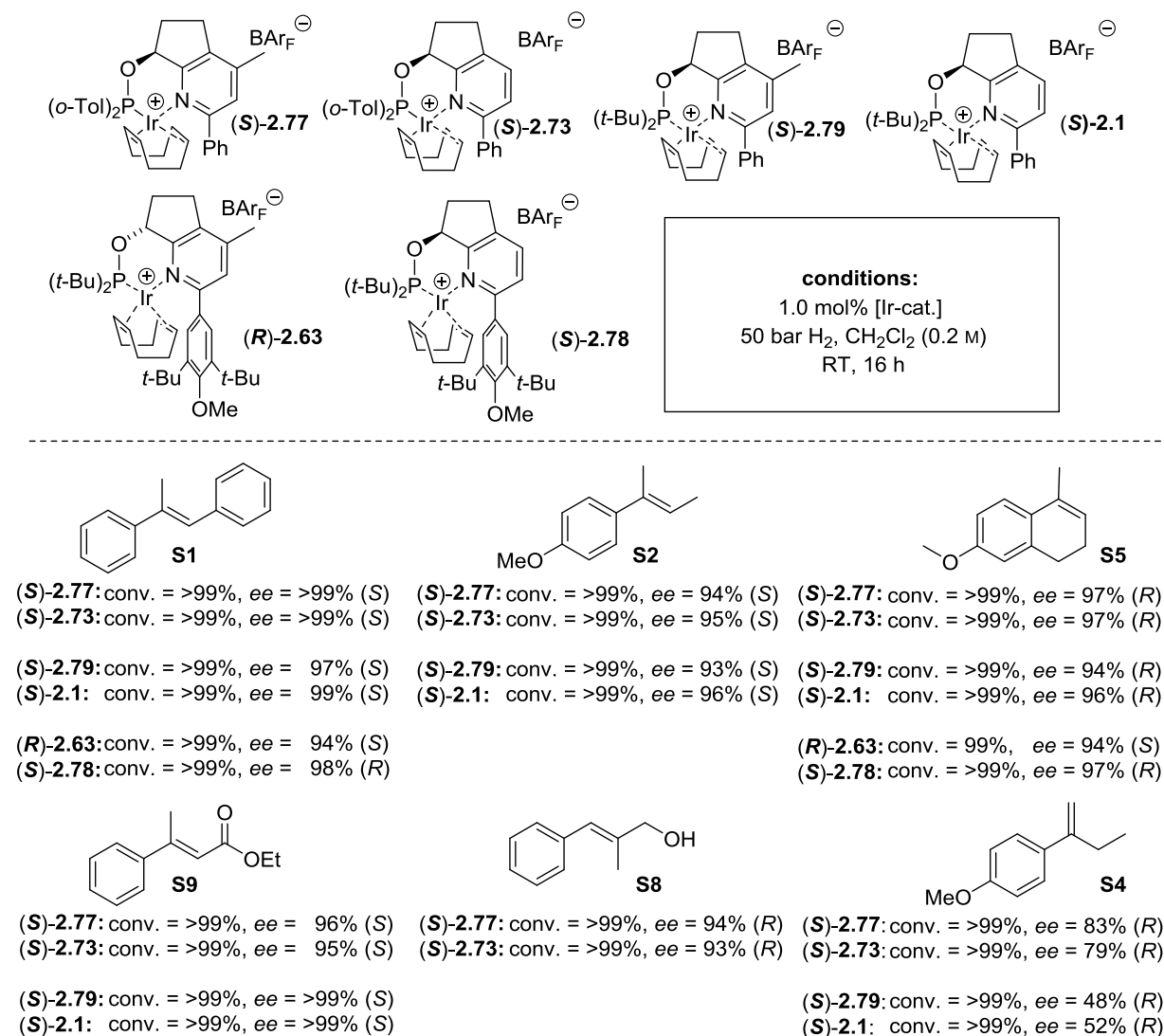
**Table 2.19:** Selected bond lengths and angles of Ir-complexes (*S*)-2.73, (*S*)-2.77, (*S*)-2.78 and (*R*)-2.63.

				
Ir-P [Å]	2.307	2.292	2.337	2.345
Ir-N [Å]	2.094	2.098	2.132	2.103
∠ P-Ir-N [°]	84.6	84.8	88.7	89.7
torsion angle plane pyridine plane aryl- substituent [°]	44.7	45.2	68.1	59.2



## 2.4.2 Hydrogenation results

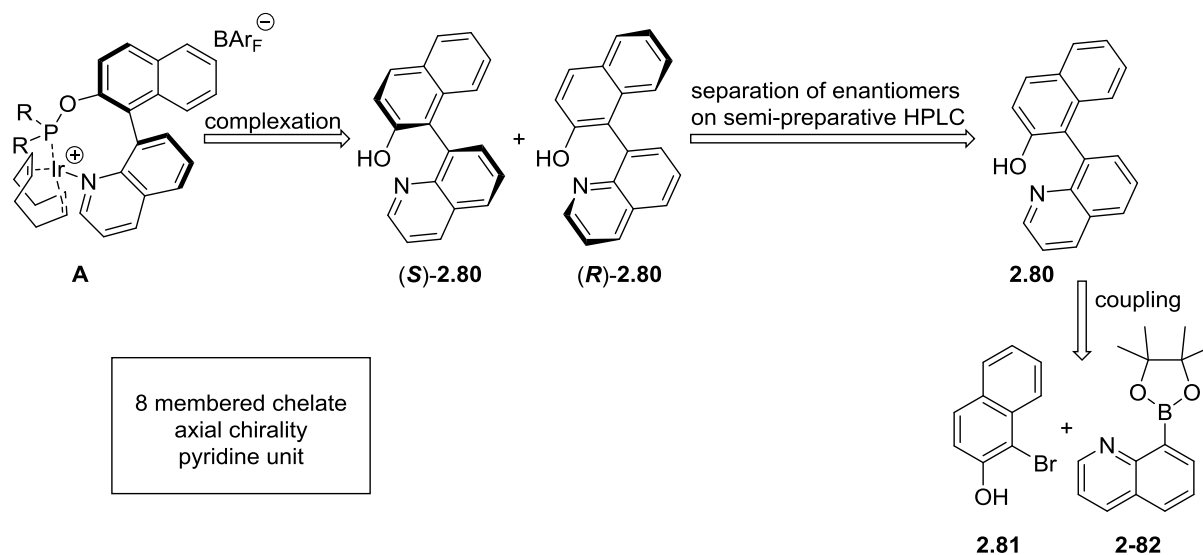
Comparing the hydrogenation results revealed predominantly similar behavior for the catalyst with and without the methyl group (scheme 2.5). However, some small differences were observed. Especially for the catalysts (**R**)-**2.63** and (**S**)-**2.78**, 94% vs. 98% *ee* and 94% vs. 97% *ee* were observed for the tested substrates. Therefore, it is not possible to exclude an influence of the methyl group.



**Scheme 2.5:** Comparison of catalysts differing only by a methyl group at the 4-position of the pyridine moiety.

## 2.5 Pyridine-based ligands with an axial chiral 8-(naphthalen-1-yl)quinoline backbone

As discussed in chapter 1, the synthesis and development of new catalysts and ligands can be seen as the fundament of any methodology dealing with catalytic transformations. A great variety of different iridium N,P ligand complexes enabling the hydrogenation of different substrate classes has been discussed so far. Nevertheless, there is still a demand for easily accessible catalysts, which can be applied to the iridium-catalyzed asymmetric hydrogenation. The number of iridium complexes forming larger chelates than six-membered rings is constantly increasing and these complexes were able to achieve excellent results in the hydrogenation of different substrate classes.<sup>[36-37, 51, 64]</sup> Also several iridium complexes containing axial chirality were successfully applied as catalysts. Having demonstrated that pyridine-based catalysts can achieve excellent enantioselectivities and reactivities in the hydrogenation of unfunctionalized double bonds, it was envisioned to synthesize iridium-based complexes of type **A**, containing an eight-membered chelate ring, axial chirality and a pyridine unit (scheme 2.6). Most importantly, these complexes should be accessible *via* a straightforward synthesis from commercially available starting materials, in only 3 steps.



**Scheme 2.6:** Retrosynthetic analysis for the preparation of iridium-based complexes of type **A**.

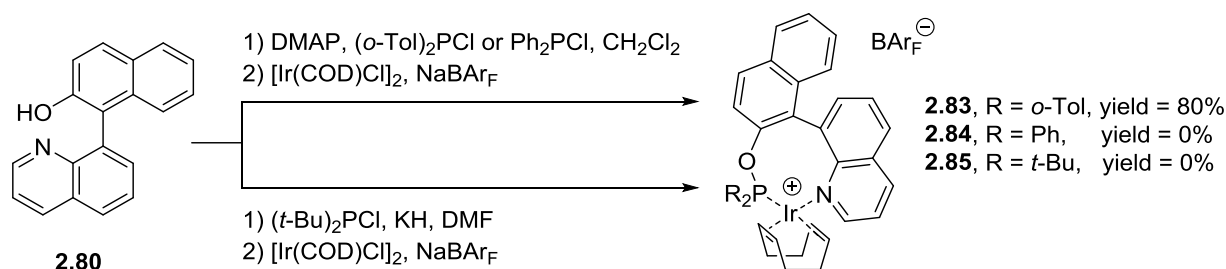
### 2.4.1 Synthesis

The Suzuki–Miyaura cross-coupling between **2.81** and **2.82** afforded 1-(quinolin-8-yl)naphthalen-2-ol (**2.80**) in poor to moderate yields (table 2.20). A maximum of 40% yield was obtained by the use of 8 mol% of (NHC)Pd(allyl)Cl (table 2.20). Although there is certainly room for improvement of this transformation, 40% yield was sufficient to investigate the next step of the reaction sequence.

**Table 2.20:** Suzuki–Miyaura cross-coupling to afford 1-(quinolin-8-yl)naphthalen-2-ol (**2.80**).

	1.0 eq.	1.2 eq.					
	<b>2.81</b>	<b>2.82</b>					<b>2.80</b>
Entry	Pd-cat.	[mol%]	Solvent	Base	Temp.	Time	Yield [%]
1		3	iso-propanol	4 M NaOH	60 °C	16 h	27
2		8	iso-propanol	4 M NaOH	60 °C	16 h	40
3		3	THF	K <sub>3</sub> PO <sub>4</sub>	25 °C	4 h	21
4	Pd(OAc) <sub>2</sub> P( <i>o</i> -Tol) <sub>3</sub>	3	toluene/ ethanol	K <sub>2</sub> CO <sub>3</sub>	100 °C	6 h	9

Next, the separation of the enantiomers of compound **2.80** by semi-preparative HPLC on a chiral stationary phase was tested. Although in an analytical scale sufficient separation of the two enantiomers was achieved, 1-(quinolin-8-yl)naphthalen-2-ol (**2.80**) showed only pure solubility in solvents which can be used for the separation. Therefore, the preparation of the corresponding iridium complexes was investigated first. By the use of previously described procedure starting from 1-(quinolin-8-yl)naphthalen-2-ol (**2.80**) (scheme 2.7), the formation of the di-*ortho*-tolylphosphinite complex **2.83** was achieved with 80% yield. However, the synthesis of the diphenylphosphinite and di-*tert*-butylphosphinite complexes failed.

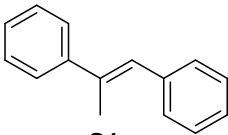
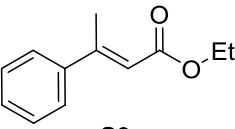
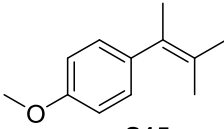
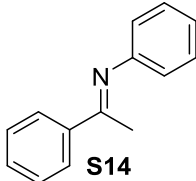


**Scheme 2.7:** Synthetic sequences for the preparation of different iridium complexes starting from 1-(quinolin-8-yl)naphthalen-2-ol (**2.80**).

## 2.4.2 Hydrogenation results

Having achieved the synthesis of complex **2.83**, its performance in the hydrogenation of different test substrates was investigated (table 2.21). This iridium complex showed in general low reactivity in the hydrogenation of C=C bonds. Only in the reduction of imine **S14** moderate reactivity was obtained.

**Table 2.21:** Hydrogenation of different substrates using catalyst **2.83**.

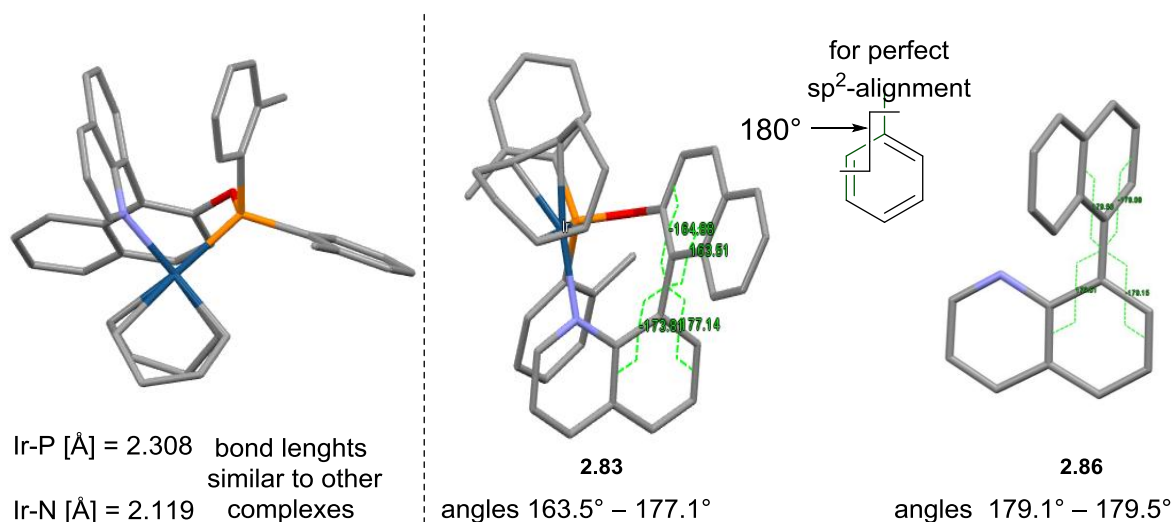
$  \begin{array}{c}  R^1 \\  \diagup \\  C \\  \diagdown \\  R^2  \end{array}  =  \begin{array}{c}  X \\  \diagup \\  C \\  \diagdown \\  R^3  \end{array}  \xrightarrow[CH_2Cl_2 (0.2 M), RT, 4 h]{0.5 \text{ mol\% } [Ir\text{-cat.}], 50 \text{ bar } H_2}  \begin{array}{c}  R^1 \\  \diagup \\  C \\  \diagdown \\  R^2  \end{array}  =  \begin{array}{c}  X \\  \diagup \\  C \\  \diagdown \\  R^3  \end{array}  $			
 <p><b>S1</b></p> <p>conv. = 1%</p>	 <p><b>S9</b></p> <p>conv. = 1%</p>	 <p><b>S15</b></p> <p>conv. = 5%</p>	 <p><b>S14</b></p> <p>conv. = 38%</p>

Conversion determined by GC on an achiral stationary phase.

With these results in hand no further studies on the performance of this catalyst were carried out in view of the crystal structure which was obtained in the course of this project.

### 2.4.3 Crystal structure of 8-(naphthalen-1-yl)quinoline-based complex **2.83**

The crystal structure of complex **2.83** showed similar Ir–N and Ir–P bond lengths as for other complexes investigated in this chapter (figure 2.6, left). However, comparing the torsion angles between two bonds which should have a value of  $180^\circ$  for an unstrained geometry, it becomes obvious that the backbone of the catalyst cannot adopt this optimal geometry. In the case of the 8-(naphthalen-1-yl)quinoline (**2.86**), representing the major part of the free ligand, the torsion angles between the bond, which bridges the naphthalene and the quinoline unit, and the other bonds which should be parallel, are in the range between  $179.1^\circ$  and  $179.5^\circ$  (figure 2.6, right). For complex **2.83** these angles deviate significantly from optimal  $180^\circ$  alignment. This deviation might be the reason why the complexation was only successful in one case and that the obtained catalyst showed in general low reactivity in the hydrogenation of C=C bonds.



**Figure 2.6:** Crystal structure of 8-(naphthalen-1-yl)quinoline-based iridium complex **2.83** and 8-(naphthalen-1-yl)quinoline as reference.

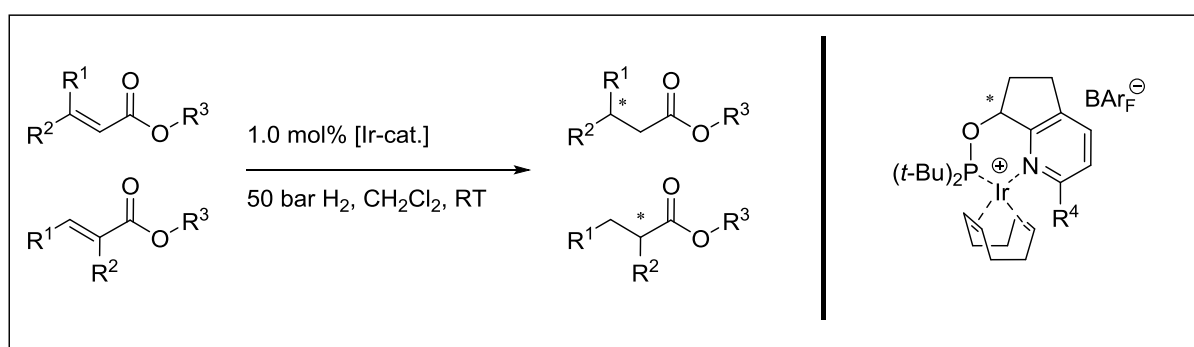
## 2.6 Summary

In summary, it was demonstrated that hindered pyridine-based N,P iridium complexes can be synthesized *via* a flexible route based on late stage derivatization to introduce the desired aryl moiety by a Suzuki–Miyaura cross-coupling. The obtained catalyst showed for several substrates higher reactivity and selectivity compared to their “parent” complexes with a phenyl group in the 2-position of the pyridine ring. Therefore, this new catalysts broaden the scope of this catalyst scaffold. In the next chapters, the applicability of these catalysts will be demonstrated in the hydrogenation of different substrate classes.

The efforts to use pyridine base catalyst with a 8-(naphthalen-1-yl)quinoline backbone were unsuccessful.

# Chapter 3

## Enantioselective Conjugated Reduction of $\alpha,\beta$ -Unsaturated Carboxylic Esters with Chiral Iridium N,P Ligand Complexes



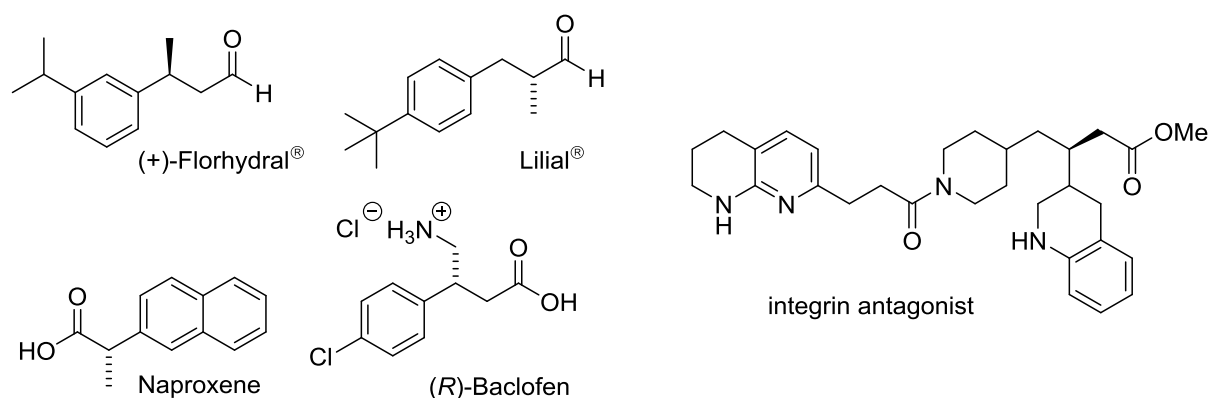
3.1 Introduction .....	65
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3.2.1 Substrate synthesis .....	68
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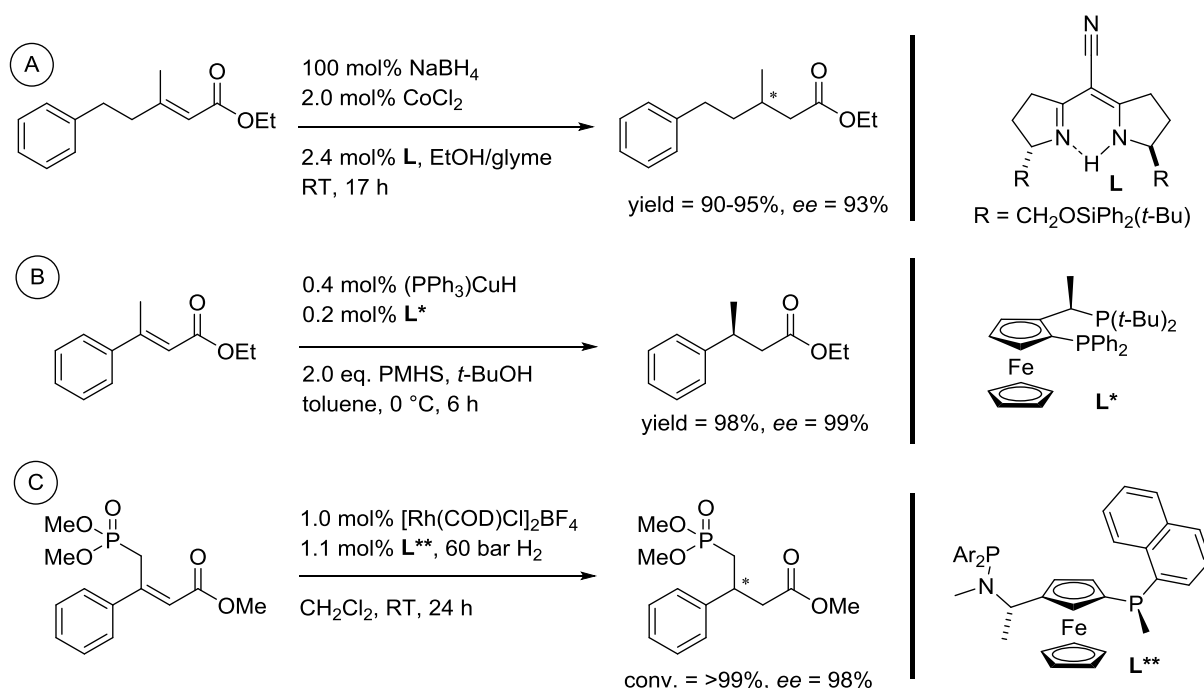
### 3.1 Introduction

The synthesis of enantiomerically enriched carboxylic esters is an important transformation leading to synthetically useful products which can be further elaborated by reactions at the ester group. Molecules accessible from such functionality are found in many natural products and many carboxylic ester derivatives that possess a tertiary stereogenic center in the  $\alpha$ - or  $\beta$ -position are known.<sup>[65]</sup> Therefore, an efficient synthesis of such enantioenriched carboxylic esters would display a highly valuable strategy towards a class of versatile building blocks and enabling the access to a variety of different compounds.



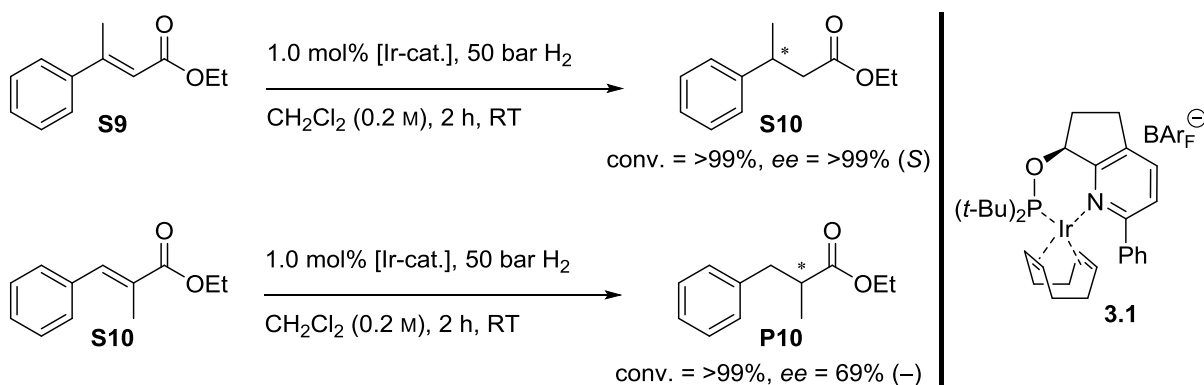
**Figure 3.1:** Selected compounds containing a tertiary stereogenic center at the  $\alpha$ - or  $\beta$ -position of an ester or ester derived functional group.

Due to the high synthetic value of this compound class, several research groups have been working on strategies to form enantiomerically enriched carboxylic esters. The conjugated reduction of  $\alpha,\beta$ -unsaturated carboxylic esters is one of them and different approaches were conducted to apply this strategy. The use of sodium borohydride and cobalt-semicorrin complexes in the conjugated reduction of  $\alpha,\beta$ -unsaturated carboxylic esters led to enantioenriched saturated esters in up to 93% *ee* (scheme 3.1, A).<sup>[66]</sup> Lipshutz and co-workers developed a chiral version of the Stryker's reagent<sup>[67]</sup> to afford saturated esters in up to 99% *ee*. However, the method required an excess of polymethylhydrosiloxane and is restricted to the generation of  $\beta$ -chiral carboxylic esters (scheme 3.1, B).<sup>[68]</sup> Also, several examples of rhodium-based catalysts in the reduction of  $\alpha,\beta$ -unsaturated esters are reported.<sup>[69]</sup> In general high enantiomeric excess is reached, but these catalysts are limited to substrates bearing an additional coordinating group such as, for example, a phosphonate (scheme 3.1, C).<sup>[70]</sup>



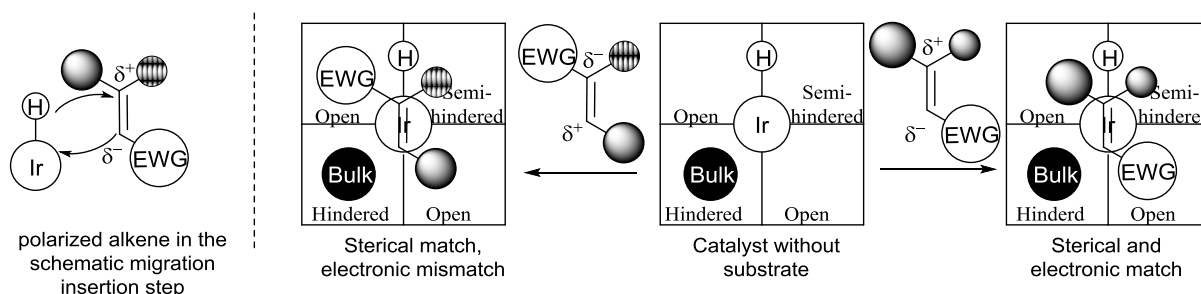
**Scheme 3.1:** Different approaches to access enantiomerically enriched carboxylic esters by conjugated reduction.

Iridium-based N,P ligand complexes, such as catalyst **3.1**, have been tested for the hydrogenation of trisubstituted  $\alpha,\beta$ -unsaturated carboxylic esters since the first reports in this field. Especially ethyl *trans*- $\beta$ -methylcinnamate (**S9**) was used as test substrate to investigate the performance of newly developed catalyst by many different research groups.<sup>[71]</sup> Although high enantioselectivity was reached for this substrate using different catalysts, other  $\alpha,\beta$ -unsaturated carboxylic esters were comparably underexplored, with poor results usually obtained for substrates with other substitution patterns than substrate **S9**. For example shifting the methyl group from the  $\beta$ - to the  $\alpha$ -position resulted in a drop of *ee* from >99% to 69% using catalyst **3.1** (scheme 3.2).<sup>[52a]</sup>



**Scheme 3.2:** Hydrogenation of ethyl *trans*- $\beta$ -methylcinnamate (**S9**) and ethyl *trans*- $\alpha$ -methylcinnamate (**S10**) with catalyst **3.1**.<sup>[52a]</sup>

In general hydrogenations of  $\alpha$ -substituted unsaturated carboxylic esters with iridium-based catalysts result in lower enantioselectivities than their  $\beta$ -substituted analogs. This behavior was explained by Andersson and co-workers on the basis of computational studies conducted on ethyl *trans*- $\beta$ -methylcinnamate (**S9**) and ethyl *trans*- $\alpha$ -methylcinnamate (**S10**). They noted, that the hydrogen transfer to the  $\alpha$ -carbon for substrate **S10** occurs *via* a sterically favored but electronically disfavored alignment. For the  $\beta$ -substituted analog the calculation showed that a sterically and electronically favored orientation in the transition state is preferred and therefore this substitution pattern usually results in higher enantioselectivities (scheme 3.3).<sup>[49]</sup> In addition, these findings were used to explain that  $\beta,\beta$ -disubstituted unsaturated carboxylic esters normally react much faster compared to their  $\alpha,\beta$ -disubstituted analogs.



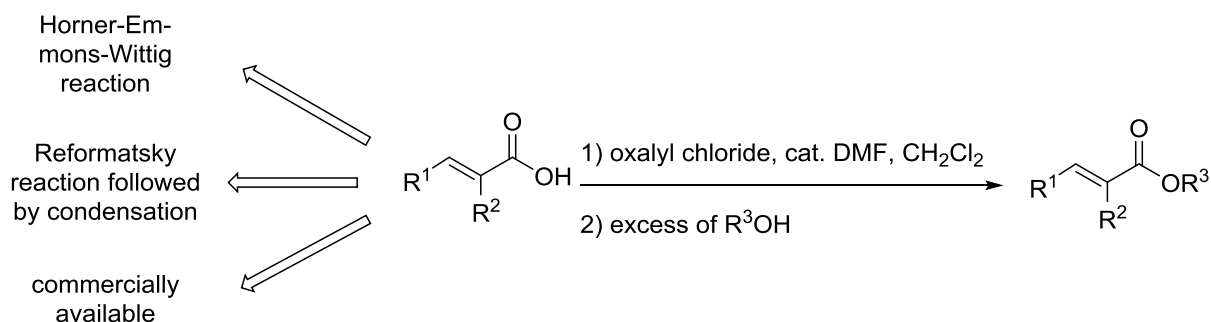
**Scheme 3.3:** Quadrant model applied by Andersson and co-workers to explain the lower enantioselectivity obtained in the hydrogenation of  $\alpha$ -substituted unsaturated esters compared to their  $\beta$ -substituted analogs.<sup>[49]</sup>

As demonstrated in chapter 2, the newly developed pyridine-based iridium N,P catalysts with a sterically demanding aryl-substituent at the 2-position of the pyridine moiety emerged as efficient catalysts in the hydrogenation of ethyl *trans*- $\alpha$ -methylcinnamate (**S10**) and *ees* up to 97% with full conversion were reached. Therefore, we conducted a detailed study on the performance of the most successful of these modular pyridine-based catalyst described in chapter 2 in the hydrogenation of different  $\alpha,\beta$ -unsaturated carboxylic esters. Additional results were obtained by Dr. D. Woodmansee or Dr. L. Tröndlin, who both worked on this project, and are included to allow for a more detailed discussion on the topic. These results are marked by a footnote (table 3.1).

## 3.2 Hydrogenation of $\alpha,\beta$ -unsaturated carboxylic esters

### 3.2.1 Substrate synthesis

All the  $\alpha,\beta$ -unsaturated esters synthesized and tested in the course of this project were produced *via* the corresponding  $\alpha,\beta$ -unsaturated carboxylic acid to allow the introduction of the different ester residues at the latest stage of the substrate synthesis (scheme 3.4). These carboxylic acids were synthesized *via* Horner–Emmons–Wittig reaction (for substrate **3.32**),<sup>[72]</sup> Reformatsky reaction<sup>[73]</sup> (for substrate **3.14**) or were commercially available (**3.2-3.5**, **S10**, **3.26-3.28** and **3.16-3.19**). Coumarin **3.36** was synthesized by condensation of 2-hydroxybenzaldehyde with phenyl acetic acid and 7-methoxy-4-methyl-2H-chromen-2-one (**3.37**) by methylation of the free alcohol. The  $\alpha,\beta$ -unsaturated esters **3.12** and **3.34** were provided by Dr. Lars Tröndlin and the  $\alpha,\beta$ -unsaturated ester (*E*)-**3.24** by Dr. Christian Ebner in our research group.



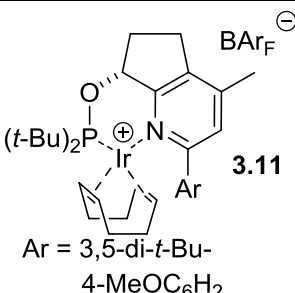
**Scheme 3.4:** Strategies employed for the synthesis of  $\alpha,\beta$ -unsaturated carboxylic esters.

## 3.2.2 Hydrogenation results

As already mentioned, the hydrogenation of  $\alpha,\beta$ -unsaturated carboxylic ester **S10** showed high selectivities of up to 97% *ee* by the use of the newly synthesized catalysts containing sterically demanding aryl groups at the 2-position of the pyridine moiety. Therefore, at the beginning of this project the influence of the different ester residues was tested by the use of the most promising catalyst bearing these modular pyridine-based ligands. For catalyst **3.10** a positive effect on the obtained enantioselectivity was achieved for ester groups with increasing steric demand. For the isopropyl ester **3.3** even 99% *ee* was obtained. Also for catalyst **3.1** the highest enantiomeric excess of 84% was obtained by the hydrogenation of the isopropyl ester analog **3.3**. Catalyst **3.11** provided *ees* in the range between 74% and 95% but no clear trends could be deduced from the data. Furthermore, for all entries full conversion was observed demonstrating the high reactivity of these catalyst towards this substrate series (table 3.1).

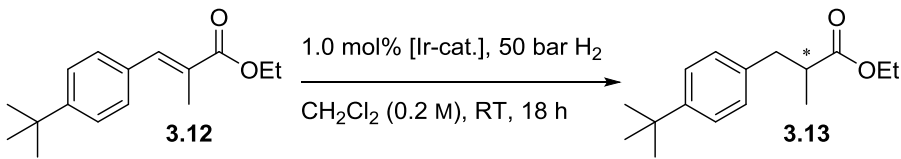
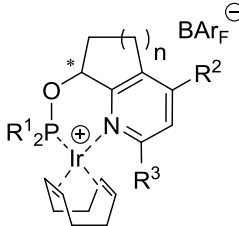
**Table 3.1:** Hydrogenation of different (*E*)- $\beta$ -methyl cinnamic esters.

<b>3.2:</b> R = Me <b>S10:</b> R = Et <b>3.5:</b> R = Hept	<b>3.3:</b> R = <i>i</i> -Pr <b>3.4:</b> R = <i>i</i> -Bu	<b>3.6:</b> R = Me <b>P10:</b> R = Et <b>3.9:</b> R = Hept	<b>3.7:</b> R = <i>i</i> -Pr <b>3.8:</b> R = <i>i</i> -Bu		
Cat.	R = Me <sup>[a]</sup> <i>ee</i> [%]	R = Et <sup>[a]</sup> <i>ee</i> [%]	R = Hept <sup>[a]</sup> <i>ee</i> [%]	R = <i>i</i> -Pr <sup>[a]</sup> <i>ee</i> [%]	R = <i>i</i> -Bu <sup>[a]</sup> <i>ee</i> [%]
 <b>3.10</b>	97 <sup>[b]</sup>	97 <sup>[b]</sup>	96	99 <sup>[b]</sup>	97
 <b>3.1</b>	46	69 <sup>[c]</sup>	78	84	75

 <b>3.11</b> Ar = 3,5-di- <i>t</i> -Bu-4-MeOC <sub>6</sub> H <sub>2</sub>	76	95	74	93	89
	[a] Reaction run on 0.1 mmol scale, full conversion was observed for all entries; [b] Measured by Dr. David Woodmansee; [c] Measured by Dr. Lars Tröndlin.				

Next the  $\alpha,\beta$ -unsaturated ester **3.12**, which is a potential precursor in the synthesis of Lilial<sup>®</sup> (see figure 3.1), was tested. This substrate proved to be unexpectedly difficult to reduce and full conversion could not be reached with 1 mol% catalyst loading with different iridium complexes using standard reaction conditions (table 3.2). Why the remote *tert*-butyl group has such a pronounced effect is unclear. Nevertheless, by the use of catalyst **3.10** 91% conversion with 94% enantiomeric excess was reached for this substrate (entry 1).

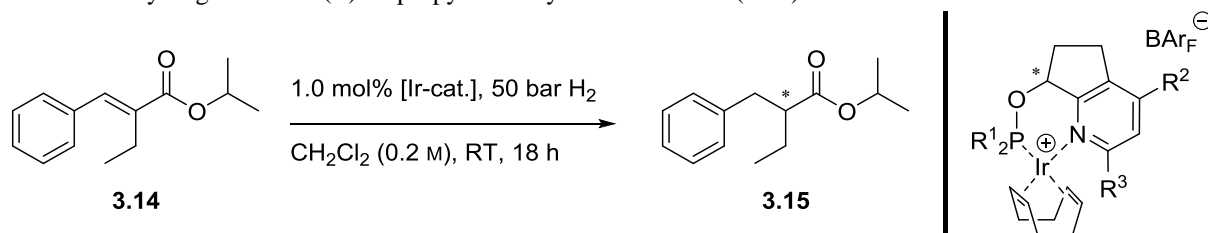
**Table 3.2:** Enantioselective hydrogenation of ethyl (*E*)-3-(4-(*tert*-butyl)phenyl)-2-methylacrylate (**3.12**).

							
							
Entry <sup>[a]</sup>	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Cat. (config.)	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[b]</sup>
1	1	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	91	94 ( <i>R</i> )
2	1	<i>t</i> -Bu	H	Ph	( <i>S</i> )	90	71 ( <i>R</i> )
3	2	<i>o</i> -Tol	H	Ph	( <i>R</i> )	49	92 ( <i>S</i> )
4	1	<i>t</i> -Bu	Me	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	63	64 ( <i>S</i> )
5	1	<i>o</i> -Tol	Me	anthracen-9-yl	( <i>S</i> )	48	82 ( <i>R</i> )

[a] Reaction on 0.1 mmol scale; [b] Determined by GC analysis on a chiral stationary phase.

In the next section, the substituent at the  $\alpha$ -position to the ester group was varied. The  $\alpha$ -ethyl-substituted ester **3.14** proved to be a more problematic substrate than the  $\alpha$ -methyl substituted analog **3.3** (table 3.3). Catalyst **3.10**, which gave so far the best results, performed only with 78% *ee* and incomplete conversion was observed (entry 1). Only catalyst **3.11** reached full conversion and with 88% *ee* still respectable enantioselectivity was obtained (entry 3).

**Table 3.3:** Hydrogenation of (*E*)-isopropyl 2-benzylidenebutanoate (**3.14**).



Entry <sup>[a]</sup>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Cat. (config.)	Conv. [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	89	78 (–)
2	<i>t</i> -Bu	H	Ph	( <i>S</i> )	36	n.d.
3	<i>t</i> -Bu	H	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	>99	88 (+)

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on a chiral stationary phase; [c] Determined by HPLC analysis on a chiral stationary phase.

Afterwards, we tested the incorporation of a phenyl group at the  $\alpha$ -position of the substrate in the asymmetric hydrogenation (table 3.4). These bulky esters proved very difficult to be reduced at 1 mol% catalyst loading and full conversion was not achieved in any of the attempted hydrogenations. However, useful levels of conversion and excellent enantioselectivity were obtained with catalyst **3.1**, which gave the saturated isopropylester with 97% *ee* and 80% conversion. The more sterically hindered complexes **3.10** showed almost no reactivity towards these substrates, which is not surprising considering the severe steric shielding of the C=C bond by the two phenyl groups. Sterically more demanding ester residues such as *tert*-butyl or 2,4-dimethyl-3-pentyl resulted in lower conversion compared to their isopropyl analog **3.17**.

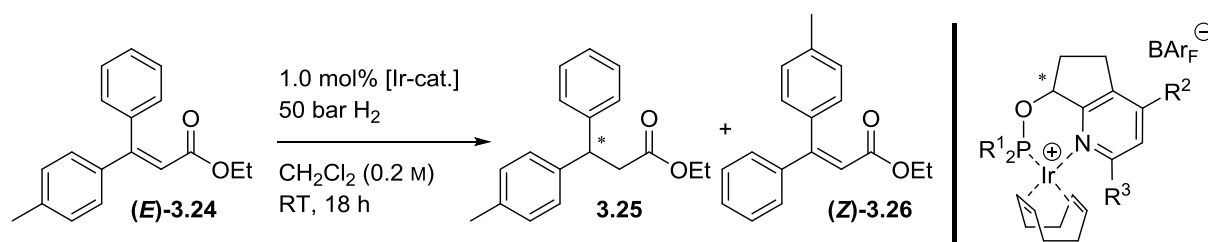
**Table 3.4:** Enantioselective hydrogenation of different (*E*)-2,3-diphenylacrylic esters.

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p> <b>3.16:</b> R = Et; <b>3.17:</b> R = <i>i</i>-Pr  <b>3.18:</b> R = <i>t</i>-Bu  <b>3.19:</b> R = 2,4-dimethyl-3-pentyl         </p> </div> <div style="text-align: center;"> <p>1.0 mol% [Ir-cat.], 50 bar H<sub>2</sub> CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), RT, 18 h</p> </div> <div style="text-align: center;"> <p> <b>3.20:</b> R = Et; <b>3.21:</b> R = <i>i</i>-Pr  <b>3.22:</b> R = <i>t</i>-Bu  <b>3.23:</b> R = 2,4-dimethyl-3-pentyl         </p> </div> </div>								
Entry <sup>[a]</sup>	R	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Cat. (config.)	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	Et	1	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	8	67 ( <i>R</i> )
2	Et	1	<i>t</i> -Bu	Me	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	90	57 ( <i>R</i> )
3	Et	1	<i>t</i> -Bu	H	Ph	( <i>S</i> )	41	89 ( <i>S</i> )
4	Et	2	<i>o</i> -Tol	H	anthracen-9-yl	( <i>R</i> )	3	39 ( <i>S</i> )
5	<i>i</i> -Pr	1	<i>t</i> -Bu	Me	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	86	82 (–)
6	<i>i</i> -Pr	1	<i>t</i> -Bu	H	Ph	( <i>S</i> )	80	97 (+)
7	<i>t</i> -Bu	1	<i>t</i> -Bu	H	Ph	( <i>S</i> )	35	n.d.
8	2,4-dimethyl-3-pentyl	1	<i>t</i> -Bu	Me	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	35 <sup>[d]</sup>	n.d.
9	2,4-dimethyl-3-pentyl	1	<i>t</i> -Bu	H	Ph	( <i>S</i> )	1	n.d.

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on a chiral stationary phase; [c] Determined by HPLC analysis on a chiral stationary phase; [d] 8% of the corresponding acid observed.

Next, we switched to the  $\beta,\beta$ -diaryl substituted  $\alpha,\beta$ -unsaturated ester (*E*)-**3.24**.  $\beta,\beta$ -Diaryl substitution is a motif which is frequently found in biologically active compounds.<sup>[74]</sup> This substrate showed moderate reactivity and a significant degree of *cis/trans* isomerization was observed in these reactions. Interestingly, although 21% isomerized product was obtained by the use of catalyst **3.1**, still 88% enantiomeric excess was observed for the hydrogenation of this substrate (table 3.5, entry 3).



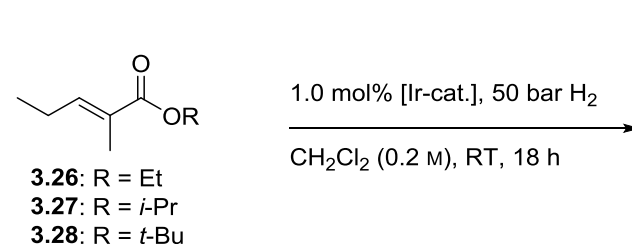
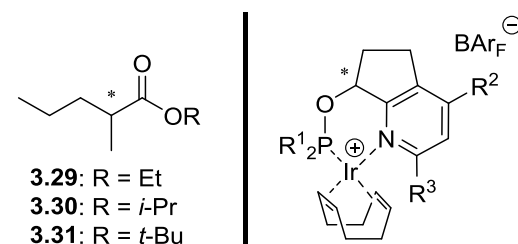
**Table 3.5:** Enantioselective hydrogenation of ethyl (*E*)-3-phenyl-3-(*p*-tolyl)acrylate ((*E*)-**3.24**).

Entry <sup>[a]</sup>	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Cat. (config.)	<b>3.25</b> [%] <sup>[b]</sup>	( <i>Z</i> )- <b>3.26</b> [%]	ee [%] <sup>[c]</sup>
1	Et	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	10	4	10
2	Et	<i>t</i> -Bu	Me	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	42	17	75
3	Et	<i>t</i> -Bu	H	Ph	( <i>S</i> )	66	21	88

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on a chiral stationary phase; [c] Determined by HPLC analysis on a chiral stationary phase.

The hydrogenation of the purely aliphatic esters **3.26–3.28** revealed in general lower enantioselectivity compared to ethyl *trans*- $\alpha$ -methylcinnamate (**S10**) (table 3.6). The enantioselectivity obtained by the use of catalyst **3.10** dropped from 97% to 71% (table 3.1 vs. table 3.6, entry 1). Notably, the remote phenyl group has a surprisingly strong effect, possibly by interaction of the  $\pi$ -system with the catalyst. The isopropyl analog **3.27** showed a similar trend as previously observed, and was reduced with a higher enantiomeric excess of 91%. The *tert*-butyl analog **3.28** was much less reactive and incomplete conversion was observed for all entries.

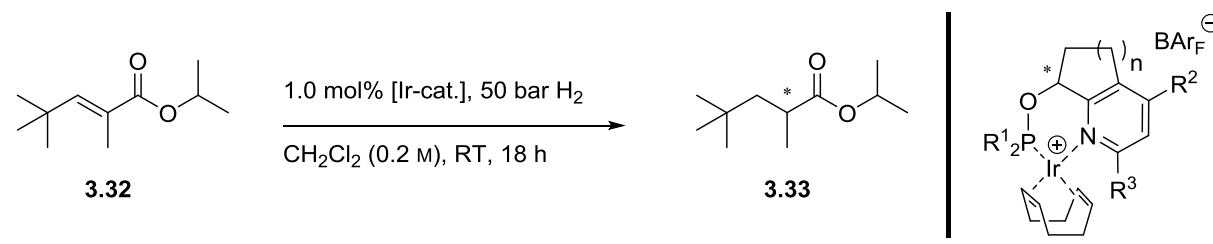
**Table 3.6:** Enantioselective hydrogenation of different (*E*)-2-methylpent-2-enoates.

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  </div> <div style="text-align: center;">  </div> </div>							
Entry <sup>[a]</sup>	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Cat. (config.)	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[b]</sup>
1	Et	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	>99	71 (–)
2	Et	<i>t</i> -Bu	H	Ph	( <i>S</i> )	>99	3 (–)
3	Et	<i>t</i> -Bu	Me	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	>99	42 (+)
4	<i>i</i> -Pr	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	>99	91 (–)
5	<i>i</i> -Pr	<i>t</i> -Bu	Me	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	>99	82 (+)
6	<i>i</i> -Pr	<i>o</i> -Tol	Me	Ph	( <i>S</i> )	>99	81 (–)
7	<i>t</i> -Bu	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	36	86 (–)
8	<i>t</i> -Bu	<i>t</i> -Bu	Me	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl	( <i>R</i> )	1	n.d.

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on a chiral stationary phase.

Isopropyl (*E*)-2,4,4-trimethylpent-2-enoate (**3.32**) turned out to be a poorly suited substrate for the pyridine-based catalyst depicted in table 3.7. A maximum of 35% enantiomeric excess and 96% conversion was reached employing catalyst **3.10** (entry 1).

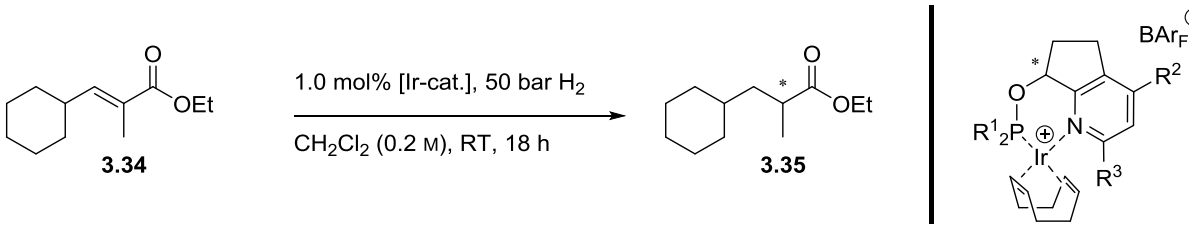
**Table 3.7:** Enantioselective hydrogenation of isopropyl (*E*)-2,4,4-trimethylpent-2-enoate (**3.32**).

							
Entry <sup>[a]</sup>	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Cat. (config.)	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[b]</sup>
1	1	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	96	35 (+)
2	1	<i>t</i> -Bu	H	Ph	( <i>S</i> )	35	n.d.
3	2	<i>o</i> -Tol	H	Ph	( <i>R</i> )	>99	27 (–)

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on a chiral stationary phase.

In the hydrogenation of ethyl (*E*)-3-cyclohexyl-2-methylacrylate (**3.35**) very low enantioselectivity was observed. Both catalysts reached full conversion but only up to 45% *ee* with catalyst **3.10** was reached in the hydrogenation reaction (table 3.8, entry 1).

**Table 3.8:** Enantioselective hydrogenation of ethyl (*E*)-3-cyclohexyl-2-methylacrylate (**3.34**).

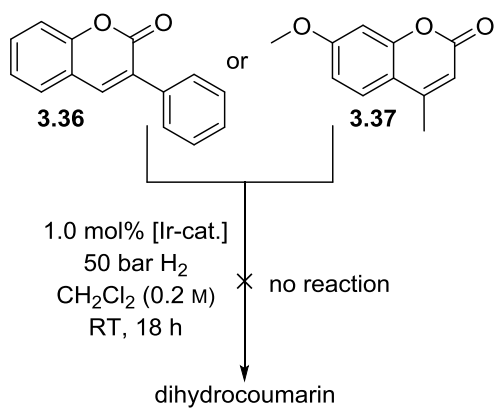
<div><div></div></div>						
Entry <sup>[a]</sup>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Cat. (config.)	Conv. [%] <sup>[b]</sup>	ee [%] <sup>[b]</sup>
1	<i>t</i> -Bu	Me	mesityl	( <i>S</i> )	>99	45 (+)
2	<i>t</i> -Bu	H	Ph	( <i>S</i> )	>99	13 (–)

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on a chiral stationary phase.

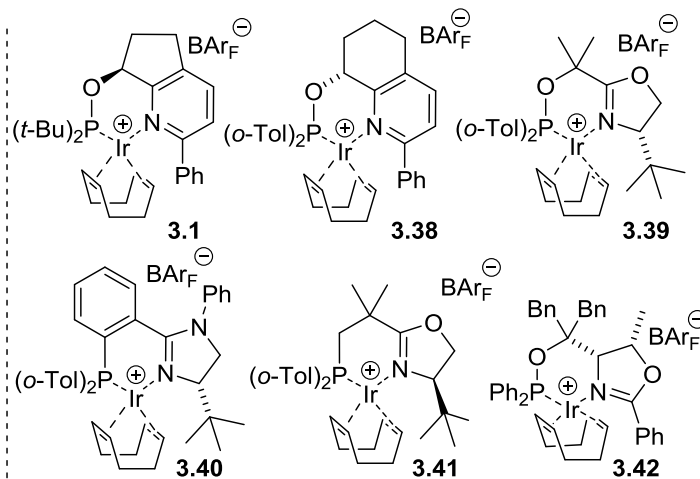
Next, we tested the applicability of coumarins **3.36** and **3.37** under the reaction conditions outlined in scheme 3.5. Based on their biological activity, dihydrocoumarins are valuable structural elements that are found in a number of different natural products.<sup>[75]</sup> In contrast to the previously tested substrates, no conversion was obtained with any of the tested catalyst

applying standard hydrogenation conditions (scheme 3.5). However, modification of the reaction parameters allowed for the reduction of these substrates (as described in chapter 6).

Different coumarins tested as substrates



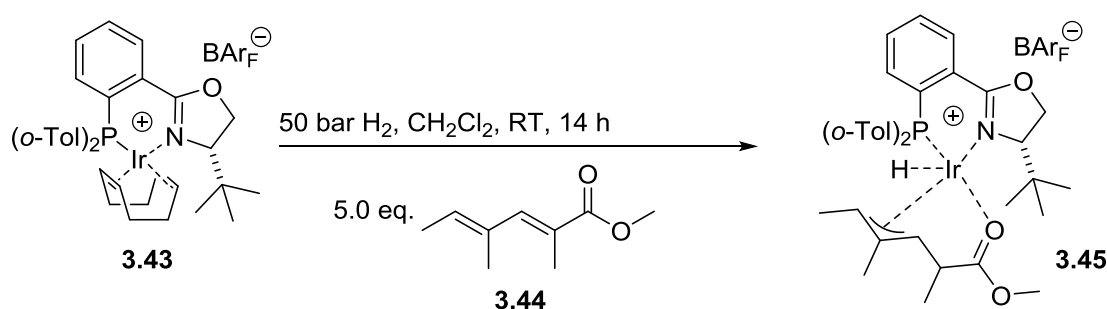
Different catalysts tested in the hydrogenation of coumarins



**Scheme 3.5:** Different catalysts that showed no reactivity in the hydrogenation of coumarins **3.36** and **3.37**.

### 3.3 Hydrogenation of dienates with sterically demanding ester groups

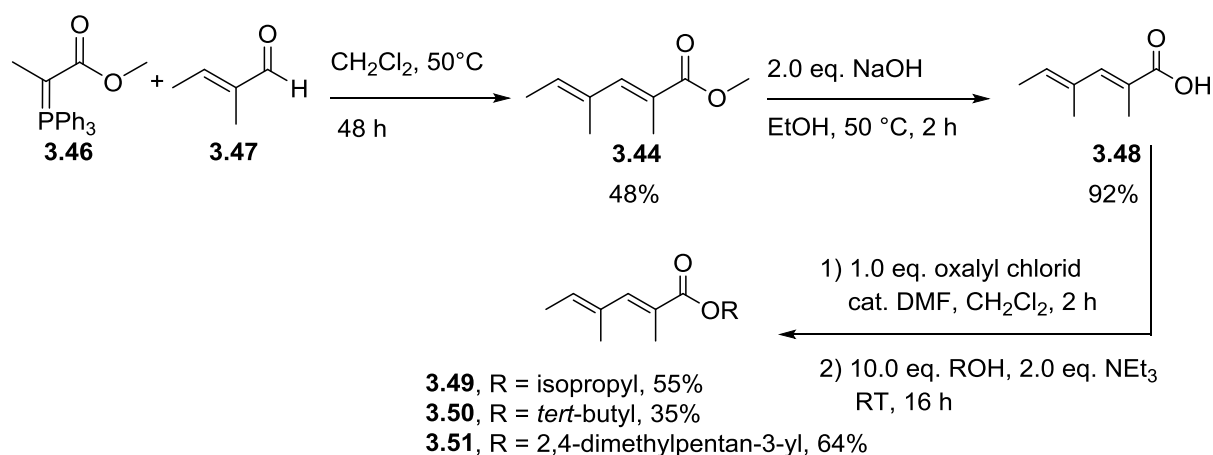
The hydrogenation of 1,3-conjugated dienes results in the formation of deoxypolyketide chirons, a structural motif frequently found in natural products.<sup>[76]</sup> The applicability of iridium-based N,P ligand complexes in the hydrogenation of such dienes was extensively studied by Dr. Andreas Schumacher in our research group.<sup>[77]</sup> In the course of this study considerable efforts were made to find a system which allows for the highly selective hydrogenation of methyl (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoate (**3.44**). The different investigated catalysts bearing N,P ligands which showed high selectivity in the hydrogenation of  $\alpha,\beta$ -unsaturated esters showed no reactivity towards this specific substrate. Such a behavior was explained by the identification and isolation of the iridium-hydride-allyl complex **3.45** formed by the reaction of iridium PHOX catalyst **3.43** in the presence of 5 eq. of substrate **3.44** under hydrogen atmosphere (scheme 3.6).



**Scheme 3.6:** Isolated iridium-hydride-allyl complex **3.45** formed in the presence of 5 eq. of substrate **3.44**.<sup>[77]</sup>

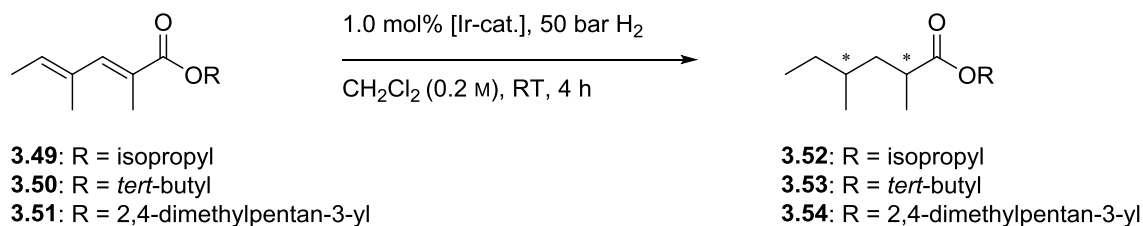
Full hydrogenation of this substrate was accomplished by the use of iridium N,P or C,N ligand complexes forming a seven-membered chelate ring. Although these catalysts enabled the reduction of this substrate, they reached only moderate enantio- and diastereoselectivities. Also other attempts conducted by Dr. Andreas Schumacher to apply six-membered iridium-based N,P ligand complexes in the hydrogenation of substrate **3.44**, such as modification of the reaction parameters (solvent, pressure or temperature), were unsuccessful. To enable the applicability of N,P ligand complexes forming a six-membered chelate ring to this substrate class, it was envisaged that a more sterically demanding ester residue would lead to a destabilization of iridium-hydride-allyl complexes such as **3.45** and thus avoid their formation or allow for a back reaction to regenerate the catalytically active species. To test this hypothesis different sterically more demanding dienates **3.49-3.51**, bearing an isopropyl-, a

*tert*-butyl- or a 2,4-dimethylpentan-3-yl-group were synthesized. The preparation of the different substrates was accomplished in 3 steps. Methyl (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoate (**3.44**) obtained by Wittig reaction was saponified to afford the carboxylic acid **3.48**, which was converted into the corresponding acyl chloride by treatment with oxalyl chloride and finally quenched with the relevant alcohol to afford the desired dienoates (scheme 3.7).



**Scheme 3.7:** Synthesis of different dienoates **3.49-3.51** with sterically demanding ester groups.

The dienoates bearing sterically demanding ester residues showed mainly low conversion similarly to their methyl analog **3.44** (table 3.9). Only for entries 13, 14 and 15 conversion to the fully saturated esters were observed. The diastereoisomeric ratio registered with a maximum of 62:38 remained poor. Interestingly, carbene catalysts **3.57** and **3.58** showed no or only moderate reactivity (23% conversion) in the hydrogenation of the methyl ester **3.44**, even using forcing reaction conditions (2 mol% catalyst loading after 14 hours in  $\text{CH}_2\text{Cl}_2$  by the use of 100 bar  $\text{H}_2$  pressure).<sup>[77]</sup> Although this concept did not allow for the application of N,P ligand complexes forming a six-membered chelate ring, it showed that the conversion can be significantly increased for catalysts which in general show reactivity for the analogous methyl ester **3.44**.

**Table 3.9:** Hydrogenation of different dienates.

Entry <sup>[a]</sup>	Cat.	R	Conv. to fully saturated ester [%] <sup>[b]</sup>	<i>dr</i> <sup>[b]</sup>
1	 <b>3.1</b>	isopropyl	0	--
2		<i>tert</i> -butyl	0	--
3		2,3,4-trimethylpentyl	0	--
4	 <b>3.55</b>	isopropyl	0	--
5		<i>tert</i> -butyl	0	--
6		2,3,4-trimethylpentyl	0	--
7	 <b>3.42</b>	isopropyl	0	--
8		<i>tert</i> -butyl	0	--
9		2,3,4-trimethylpentyl	0	--
10	 <b>3.56</b>	isopropyl	decomposition	--
11		<i>tert</i> -butyl	decomposition	--
12		2,3,4-trimethylpentyl	decomposition	--
13	 <b>3.57</b>	isopropyl	>99	57:43
14		<i>tert</i> -butyl	decomposition	--
15		2,3,4-trimethylpentyl	>99	62:38
16	 <b>3.58</b>	isopropyl	53	n.d.
17		<i>tert</i> -butyl	decomposition	--
18		2,3,4-trimethylpentyl	decomposition	--

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on a chiral stationary phase.

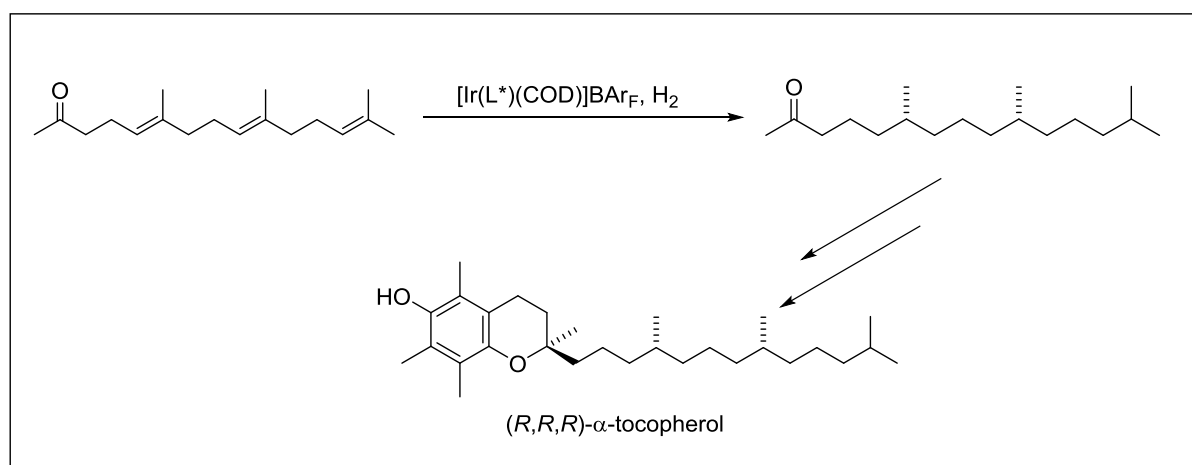
### 3.4 Conclusion

The high enantioselectivities obtained in the hydrogenation of various  $\alpha,\beta$ -unsaturated carboxylic esters with aryl or alkyl substituents at the C=C bond show that iridium complexes derived from chiral N,P ligands are efficient catalysts for this transformation. By changing the substitution pattern around the C=C bond and the ester moiety, different activities and selectivities were observed. As expected, none of the complexes that were evaluated emerged as a universal catalyst. Depending on the substitution pattern of the substrate, different ligands performed best. For instance, iridium complex **3.1** was superior for more sterically demanding substrates, whereas complex **3.11** showed the best results towards substrates with less sterically demanding substituents around the C=C bond. This highlights the advantage of a modular approach to the synthesis of catalysts and the need for such catalysts with tunable steric and electronic properties. The results outlined above also show that  $\alpha,\beta$ -unsaturated carboxylic esters substituted at the  $\alpha$ -position are less problematic substrates than originally anticipated based on previous studies. Furthermore, it was possible to transfer the results obtained in the hydrogenation of  $\alpha,\beta$ -unsaturated carboxylic esters to dienoates. Unfortunately, high selectivity could not be achieved. However, significantly higher conversion in the hydrogenation of the isopropylester analog **3.49** was achieved for catalysts which previously demonstrated only low reactivity for this substrate class.



## Chapter 4

### Asymmetric Hydrogenation of Tocopherol Side Chain Precursors

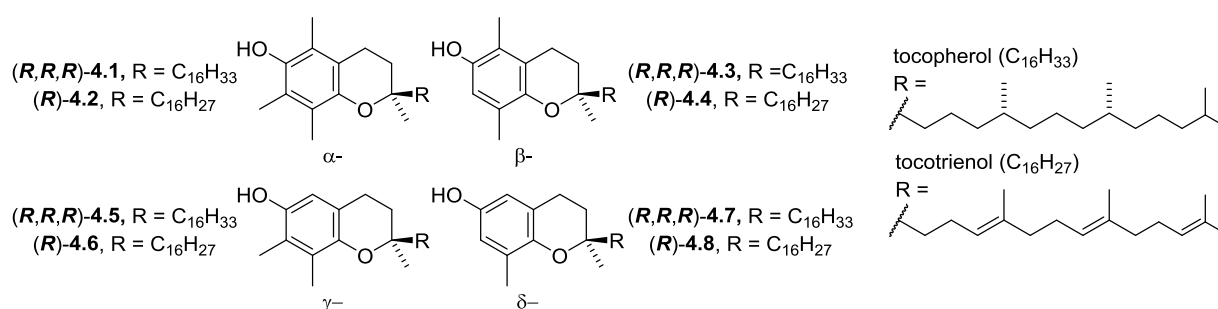


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#### 4.1 Towards a stereoselective large scale synthesis of (R,R,R)- $\alpha$ -tocopherol

The term vitamin E refers to a group of eight lipophilic isomeric tocopherol- and tocotrienol-derivatives. Their nomenclature depends on the degree of methylation of the chromanol unit and the nature of the side chain, as summarized figure 4.1.<sup>[78]</sup> Among these molecules,  $\alpha$ -tocopherol (**4.1**) is the most common and based on its increased biological activity also the most studied molecule of the vitamin E family.



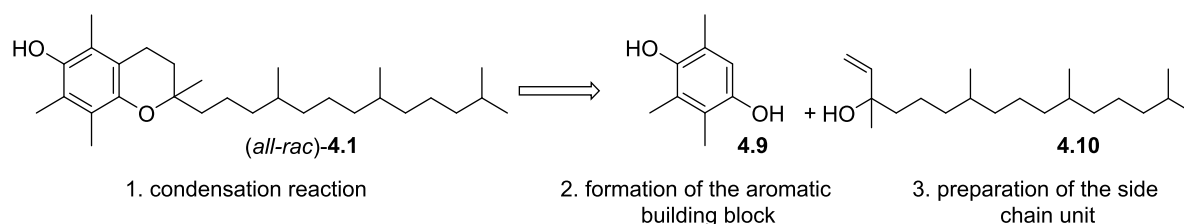
**Figure 4.1:** All eight members of the vitamin E family.

It was found that the different compounds of vitamin E show anti-inflammatory activity and are also considered as the most important lipid-soluble antioxidants in biological systems.<sup>[79]</sup> These and other properties led to different studies, conducted mainly on  $\alpha$ -tocopherol proposing the benefit to mitigate cardiovascular disease, promoting plasma membrane repair and slowing Alzheimer's disease progression.<sup>[80]</sup> From an industrial point of view, the most relevant product of this class is (*all-rac*)- $\alpha$ -tocopherol ((*all-rac*)-**4.1**), which represents an equimolar mixture of all eight stereoisomers of  $\alpha$ -tocopherol, and exceeds a production of 30000 tons per year worldwide and is constantly increasing.<sup>[81]</sup> In the USA the recommended dietary allowance for adults is set to 15 mg/day for (*R,R,R*)- $\alpha$ -tocopherol ((*R,R,R*)-**4.1**).<sup>[82]</sup> The naturally occurring (*R,R,R*)-stereoisomer of  $\alpha$ -tocopherol is approximately twice as biologically active in adults than its synthetic form, (*all-rac*)- $\alpha$ -tocopherol.<sup>[83]</sup> Hence, already in 1963 the research group of Isler published the first synthesis of the (*R,R,R*)-stereoisomer.<sup>[84]</sup> Nowadays roughly 10% of the industrially produced vitamin E consists of  $\alpha$ -tocopherol in its isomerically pure (*R,R,R*) configuration which is produced in a semisynthetic way starting from soya deodorizer distillates, a waste stream from the production of the corresponding

vegetable oil.<sup>[79]</sup> However, higher quantities of (*R,R,R*)- $\alpha$ -tocopherol ((*R,R,R*)-**4.1**) are not accessible due to insufficient amounts of natural source starting material.<sup>[85]</sup>

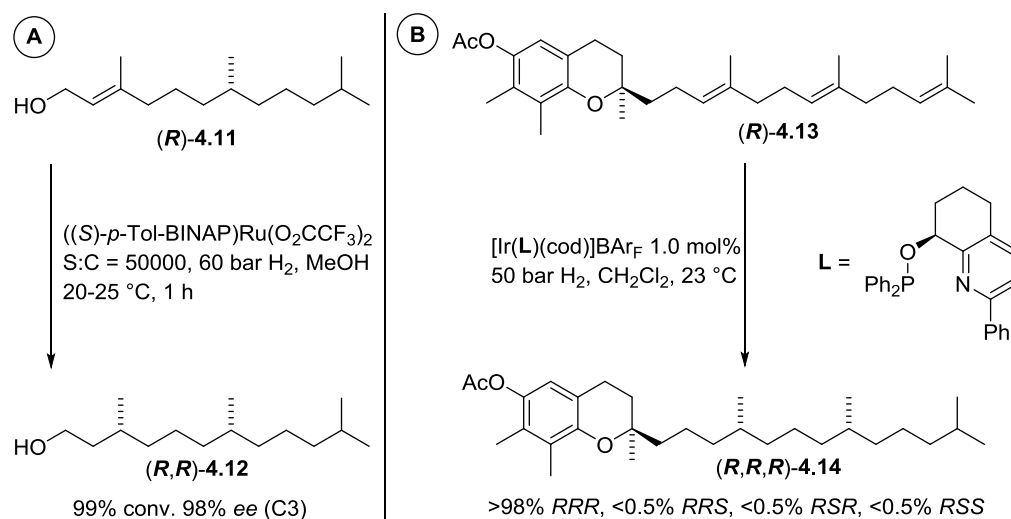
Over the last years, extensive efforts to accomplish an efficient and stereoselective synthesis of (*R,R,R*)- $\alpha$ -tocopherol and its building blocks were made. These approaches were based on auxiliary-controlled reactions, the use of starting material from the chiral pool, optical resolution of the product, desymmetrization and asymmetric bio- and transition metal-catalysis.<sup>[84, 86]</sup> However, so far all these procedures do not fulfill the demands required for a large scale industrial production, as they suffer from complexity, limited space-time yield or high E-factors.<sup>[79]</sup>

An alternative approach could be represented by a modification of the highly optimized industrial route to (*all-rac*)- $\alpha$ -tocopherol ((*all-rac*)-**4.1**) in order to allow for the enantioselective generation of the stereogenic centers. This route can be mainly divided in 3 parts: 1) the final condensation reaction, 2) the formation of the aromatic building block **4.9** and 3) the preparation of the isopytol side chain **4.10** (scheme 4.1).



**Scheme 4.1:** Strategic disconnection in the industrial synthesis of (*all-rac*)- $\alpha$ -tocopherol ((*all-rac*)-**4.1**).

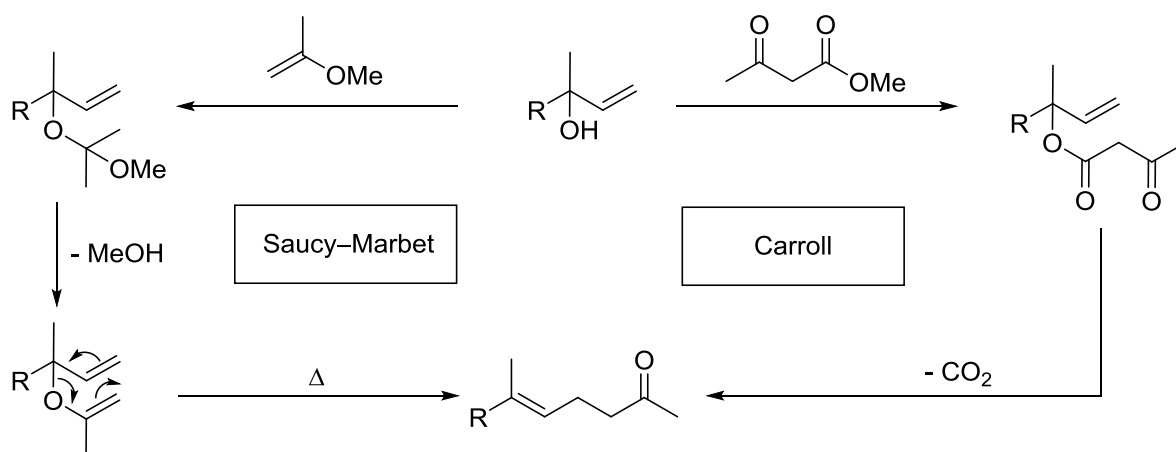
With the application of asymmetric hydrogenation significant progress has been made in the stereoselective generation of the stereogenic centers in the phytyl tail **4.10**. Based on the seminal work by Noyori and co-workers, Roche published on the hydrogenation of the side chain mimic (*R,E*)-3,7,11-trimethyldodec-2-en-1-ol ((*R*)-**4.11**) by the use of ((*S*)-*p*-Tol-BINAP)Ru(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub>. The reaction was performed with a substrate to catalyst ratio of 50000, reaching 99% conversion and an enantiomeric excess of 98% (C3) within only one hour of reaction time (scheme 4.2, A).<sup>[87]</sup> Catalysts of this type usually require a coordinating group in close proximity to the target double bond, as in the case of the alcohol (*R*)-**4.11**. Therefore, an approach based on the use of ruthenium catalysts would imply a stepwise construction of the side chain with two asymmetric hydrogenation steps to be carried out. In addition, the required prochiral allylic alcohols are not direct intermediates in the industrially applied syntheses.



**Scheme 4.2:** Strategies to apply asymmetric hydrogenation to the generation of an enantiopure side chain.

In contrast to ruthenium-based catalysts, N,P ligand-based iridium complexes emerged as efficient catalysts for the asymmetric hydrogenation of unfunctionalized double bonds. Taking advantage from this property of such iridium-catalysts, DSM Nutritional Products and the Pfaltz research group were able to obtain almost exclusively (*all-R*)- $\gamma$ -tocopheryl acetate ((*R,R,R*)-**4.14**) by the application of a chiral pyridyl phosphinite-based iridium catalyst. The hydrogenation of the precursor (*R*)-**4.13** resulted in the introduction of two stereogenic centers and the reduction of three double bonds in a single reaction step (scheme 4.2, B).<sup>[53c]</sup> In a later publication the high efficiency of this catalyst for the generation of the desired stereoisomer in high enantiomeric purity from different geometric isomers of farnesol was also successfully demonstrated.<sup>[53b]</sup>

As previously mentioned, the synthesis of the tocopherol side-chain is an important part in the production of vitamin E and is conducted by using various approaches in industry. In principle, these strategies are mainly based on a combination of C3 and C2 elongations starting from acetone or citral. Specific reaction types involved therein are ethynylation of ketones, Lindlar type hydrogenations, aldol condensations, Prins reaction and Saucy–Marbet or Carroll reactions. The latter two result in the formation of prochiral  $\gamma,\delta$ -unsaturated ketones. These intermediates are potential targets for the selective introduction of the stereogenic centers embedded in the tocopherol side chain (scheme 4.3).



**Scheme 4.3:** Saucy-Marbet and Carroll reaction applied for the C3-elongation steps in the synthesis of tocopherol.

Therefore, the applicability of chiral Ir-N,P ligand complexes to the hydrogenation of these intermediates was investigated in cooperation with DSM Nutritional Products and results are described in this chapter.

## 4.2 General information about the hydrogenation project

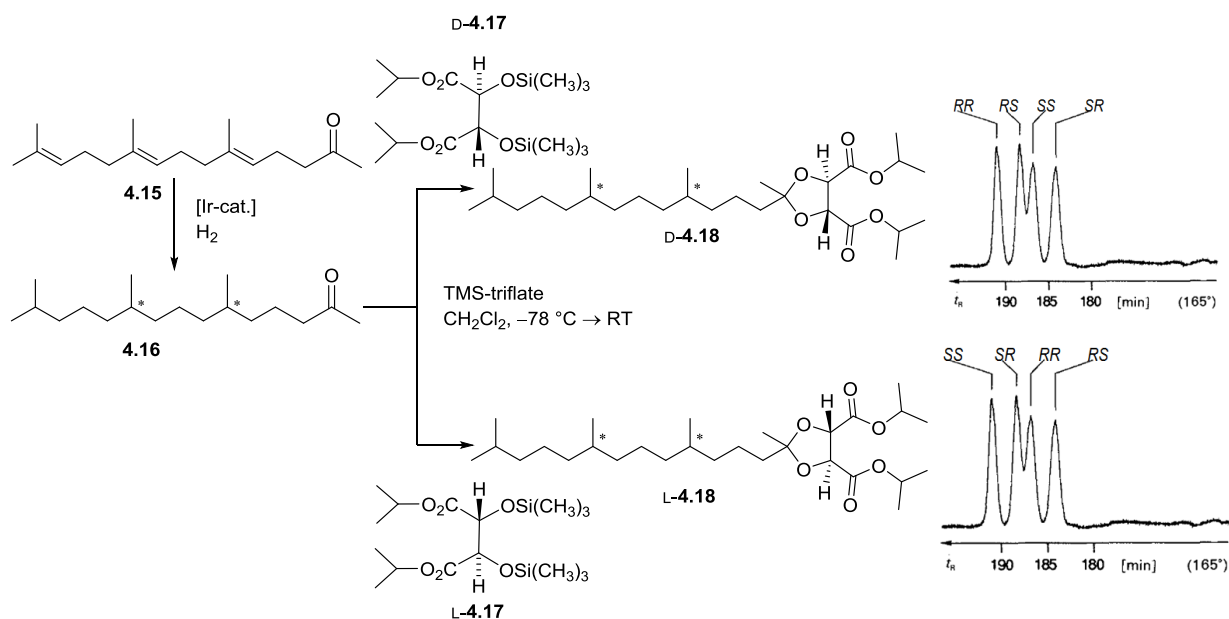
### 4.2.1 Supply of substrates

The substrates investigated within this chapter were all provided by DSM and consist of  $\gamma,\delta$ -unsaturated ketones with different chains lengths, different double bond geometries and different degrees of saturation (figure 4.4).

### 4.2.2 Analysis of the hydrogenation products

The conversion of the reactions was determined by GC using an achiral stationary phase. In the majority of the experiments the conversion to the fully reduced hydrogenation product or the amount of the remaining starting material is given.

At the outset of this project, the amount of the different stereoisomers formed was determined by GC using a chiral stationary phase. For this purpose, the fully reduced farnesylacetone was derivatized with L- or D-diisopropyl tartrate (L-**4.17** and D-**4.17**) and analyzed following the literature procedure reported by A. Knierzinger *et al.*<sup>[88]</sup> This allowed for the determination of the major stereoisomer by using the corresponding tartrate for derivatization. Full assignment of all four stereoisomers can be done by an additional derivatization and analysis using the tartrate in its opposite configuration (scheme 4.4), but due to the time-consuming analysis of the selectivity the focus was laid on the determination of the amount of the major stereoisomer which gave sufficient data for the identification of the most selective catalysts. The selectivity was not determined for reactions showing incomplete conversion, as in this case, up to 20 different species could be formed and as a consequence overlapping signals were observed in the gas chromatogram. In these cases an accurate determination of the selectivity was therefore impossible.



**Scheme 4.4:** Analytic method for the determination of the selectivity of the reaction (GC traces incorporated from Knierzinger *et al.*<sup>[88]</sup>).

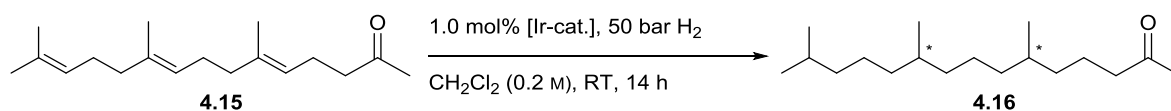
During the course of this cooperation improved analytical methods for the direct determination of the different stereoisomers were developed by DSM.<sup>[89]</sup> When the specific amount of all four stereoisomers was assigned, the selectivity was determined at DSM. Again, the selectivity could not be determined for reactions showing incomplete conversion.

## 4.3 Optimization of the reaction conditions

### 4.3.1 Catalyst screening

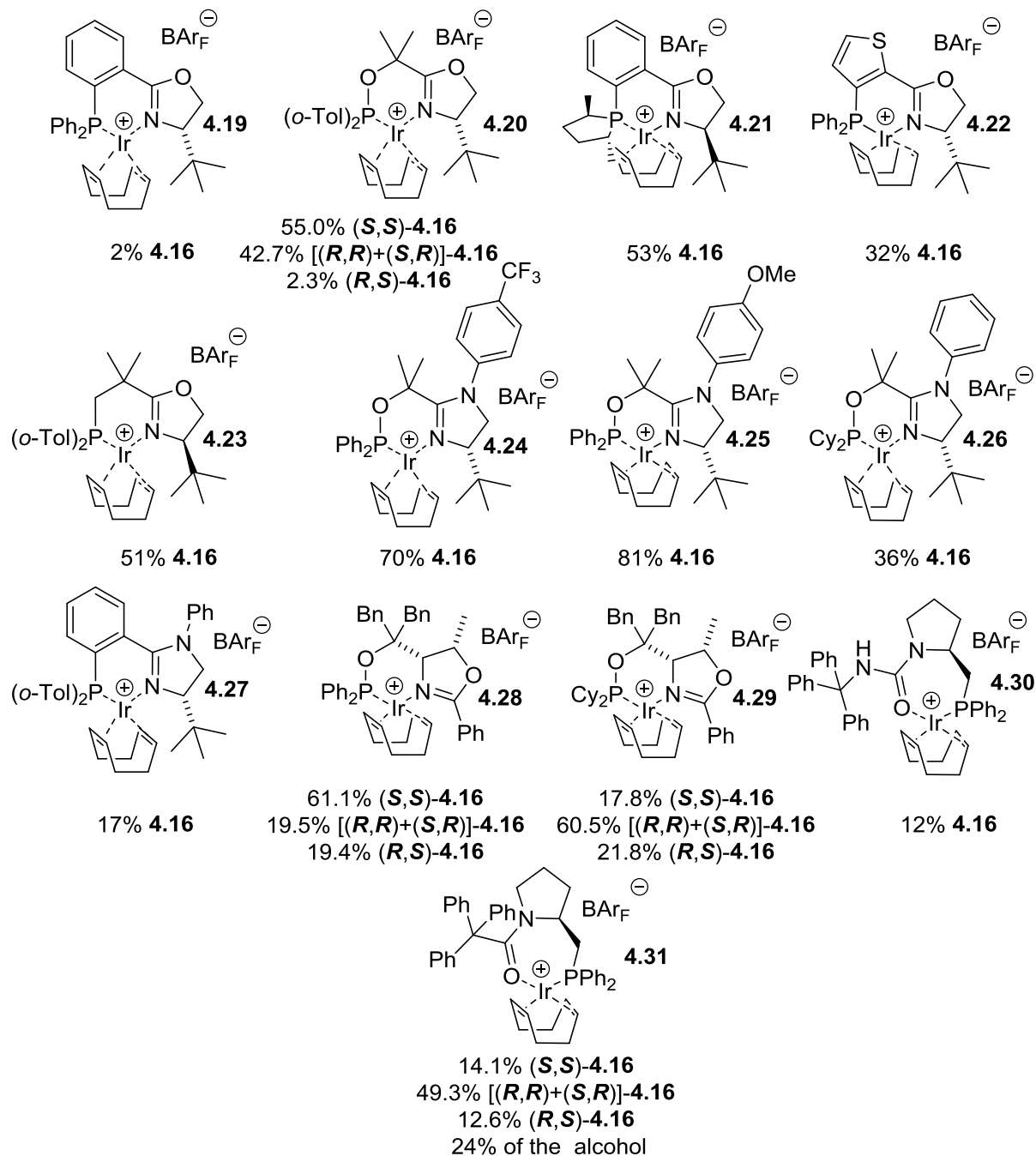
The hydrogenation of (5*E*,9*E*) farnesylacetone (**4.15**), which from an industrial perspective is the most relevant and therefore most important intermediate for the synthesis of vitamin E, served as a starting point for this study. First the most selective catalysts for the hydrogenation of this substrate had to be identified and then used for the optimization of the reaction conditions. Therefore, different catalyst scaffolds were investigated and a detailed study of the most promising ones was conducted. The catalysts were divided in non-pyridine and pyridine-based complexes, to allow for a systematic classification. Hydrogenations were conducted under reaction conditions which previously emerged as efficient for many different substrate classes: 1.0 mol% catalyst loading, 50 bar H<sub>2</sub> pressure, CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), room temperature, 14 hours (see scheme 4.5).





**Scheme 4.5:** General reaction conditions applied to the catalyst screening of (5E,9E)-farnesylacetone (**4.15**).

#### 4.3.1.1 Screening of non-pyridine-based catalysts

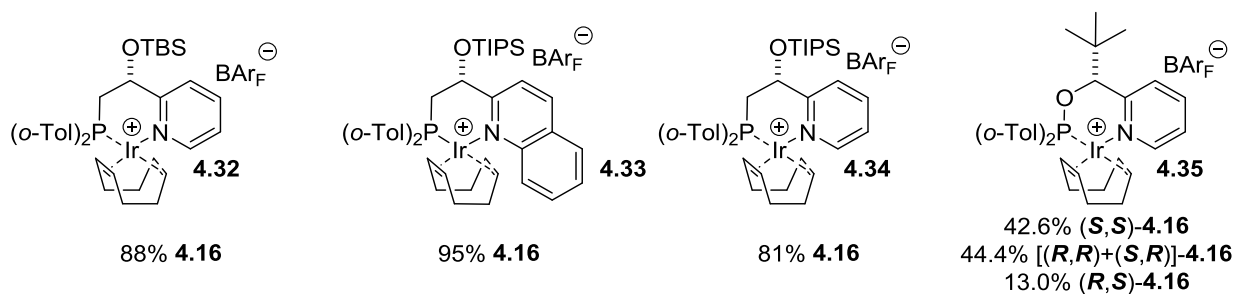


**Table 4.1:** Non-pyridine-based catalyst in the hydrogenation of (5E,9E)-farnesylacetone (**4.15**) (reaction conditions: 0.2 mmol substrate, 1.0 mol% catalyst loading, 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), RT, 14 h).

For the majority of the catalysts tested complete conversion to the fully reduced substrate **4.16** was not observed. Only four catalysts (**4.20**, **4.28**, **4.29**, **4.31**) provided full conversion, but in

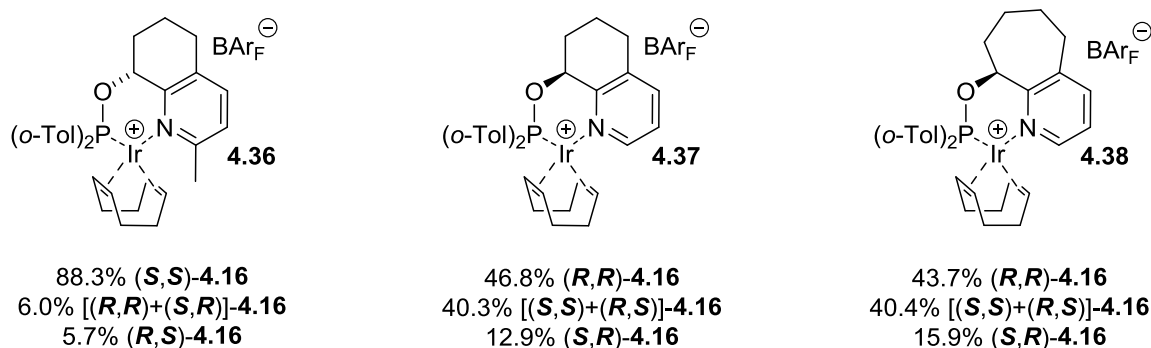
each case only low selectivity was observed (table 4.1). Catalysts **4.28** and **4.29** bearing a phosphinite moiety showed even inverted selectivity for the preferred stereoisomer.

#### 4.3.1.2 Screening of pyridine-based catalysts



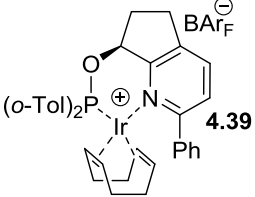
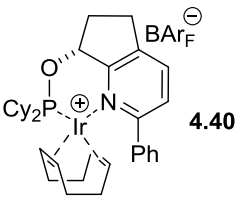
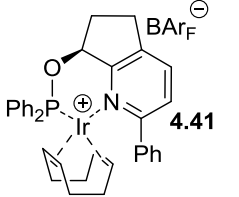
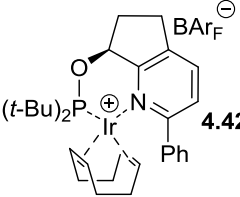
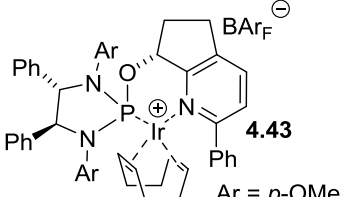
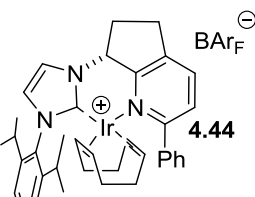
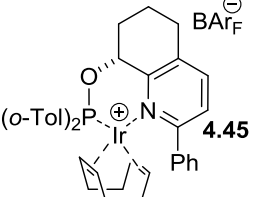
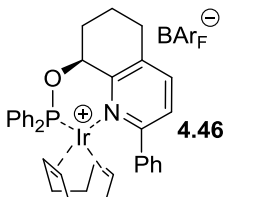
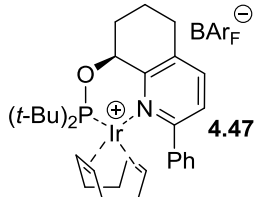
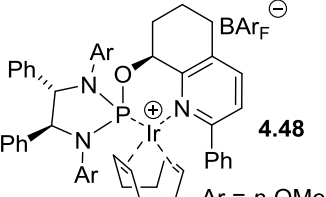
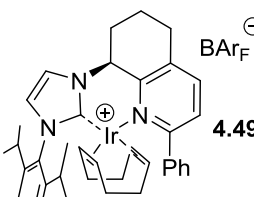
**Table 4.2:** Pyridine-based catalysts in the hydrogenation of (*5E,9E*)-farnesylacetone (reaction conditions: 0.2 mmol substrate, 1.0 mol% catalyst loading, 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), RT, 14 h).

With all the catalysts of this series bearing a phosphine moiety incomplete conversion to the fully reduced product was observed. Only catalyst **4.35**, featuring a phosphinite group, afforded full conversion to ketone **4.16** but low selectivity (table 4.2).



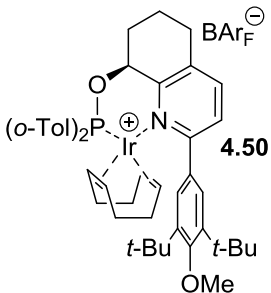
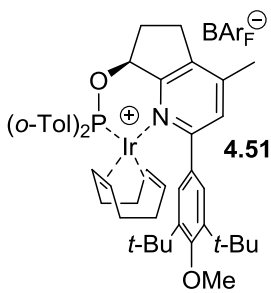
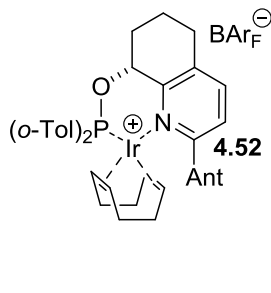
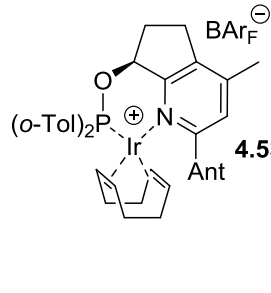
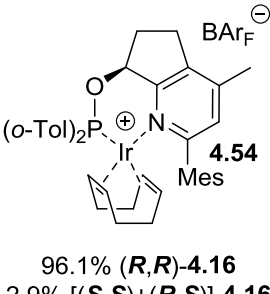
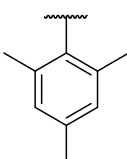
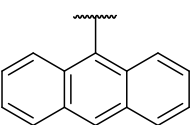
**Table 4.3:** Bicyclic pyridine-based catalyst in the hydrogenation of (*5E,9E*)-farnesylacetone (reaction conditions: 0.2 mmol substrate, 1.0 mol% catalyst loading, 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), RT, 14 h).

Pyridine-based catalysts bearing an additional aliphatic ring showed full conversion in all cases. Methyl substitution at the 2-position revealed a selectivity of 88.3% for the major stereoisomer and showed the significant impact of this position on the selectivity (table 4.3).

 <p>4.39</p> <p>84.0% (<i>R,R</i>)-4.16 14.2% [(<i>S,S</i>)+(<i>R,S</i>)]-4.16 1.8% (<i>S,R</i>)-4.16</p>	 <p>4.40</p> <p>90.0% (<i>S,S</i>)-4.16 4.2% [(<i>R,R</i>)+(<i>S,R</i>)]-4.16 5.8% (<i>R,S</i>)-4.16</p>	 <p>4.41</p> <p>96.4% (<i>R,R</i>)-4.16 1.8% [(<i>S,S</i>)+(<i>R,S</i>)]-4.16 1.8% (<i>S,R</i>)-4.16</p>	 <p>4.42</p> <p>92.9% (<i>R,R</i>)-4.16 2.3% [(<i>S,S</i>)+(<i>R,S</i>)]-4.16 4.8% (<i>S,R</i>)-4.16</p>
 <p>4.43</p> <p>Ar = <i>p</i>-OMe</p> <p>89.2% (<i>S,S</i>)-4.16 7.7% [(<i>R,R</i>)+(<i>S,R</i>)]-4.16 3.1% (<i>R,S</i>)-4.16</p>	 <p>4.44</p> <p>43.3% (<i>S,S</i>)-4.16, 23.6% (<i>S,R</i>)-4.16 20.3% (<i>R,S</i>)-4.16, 12.9% (<i>R,R</i>)-4.16 2.0 mol% cat. loading</p>	 <p>4.45</p> <p>96.6% (<i>S,S</i>)-4.16 1.2% [(<i>R,R</i>)+(<i>S,R</i>)]-4.16 2.2% (<i>R,S</i>)-4.16</p>	 <p>4.46</p> <p>90.2% (<i>R,R</i>)-4.16 1.2% [(<i>S,S</i>)+(<i>R,S</i>)]-4.16 8.6% (<i>S,R</i>)-4.16</p>
 <p>4.47</p> <p>50.1% (<i>R,R</i>)-4.16 17.3% [(<i>S,S</i>)+(<i>R,S</i>)]-4.16 32.6% (<i>S,R</i>)-4.16</p>	 <p>4.48</p> <p>Ar = <i>p</i>-OMe</p> <p>92.2% (<i>R,R</i>)-4.16 1.6% [(<i>S,S</i>)+(<i>R,S</i>)]-4.16 6.2% (<i>S,R</i>)-4.16</p>	 <p>4.49</p> <p>43.3% (<i>S,S</i>)-4.16, 23.6% (<i>S,R</i>)-4.16 20.3% (<i>R,S</i>)-4.16, 12.9% (<i>R,R</i>)-4.16 2.0 mol% cat. loading</p>	

**Table 4.4:** Bicyclic, phenyl substituted pyridine-based catalysts in the hydrogenation of (*5E,9E*)-farnesylacetone; reaction conditions: 0.2 mmol substrate, 1.0 mol% catalyst loading, 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), RT, 14 h). Complete conversion was obtained for all entries.

All catalysts of this series, bearing a phenyl substituent at the 2-position of the pyridine moiety, reached complete conversion to the fully reduced substrate and revealed good to excellent selectivities. There was no general trend observed for the ring size in the backbone of the ligand scaffold and the phosphinite moiety. The more rigid catalyst scaffolds, bearing an aliphatic five-membered ring, seemed to be less sensitive to structural changes in the phosphinite unit. The replacement of the phosphinite by a carbene resulted in incomplete conversion at 1.0 mol% catalyst loading and significantly reduced selectivity at 2.0 mol% catalyst loading. Complex **4.45** emerged as the most selective catalyst within this series, enabling the formation of 96.6% of the desired stereoisomer (table 4.4).

 <p>89.6% (<i>R,R</i>)-<b>4.16</b> 2.0% [(<i>S,S</i>)+(<i>R,S</i>)]-<b>4.16</b> 8.4% (<i>S,R</i>)-<b>4.16</b></p>	 <p>83.8% (<i>R,R</i>)-<b>4.16</b> 7.1% [(<i>S,S</i>)+(<i>R,S</i>)]-<b>4.16</b> 9.1% (<i>S,R</i>)-<b>4.16</b></p>	 <p>97.4% (<i>S,S</i>)-<b>4.16</b> 0.5% [(<i>R,R</i>)+(<i>S,R</i>)]-<b>4.16</b> 2.1% (<i>R,S</i>)-<b>4.16</b></p>	 <p>98.5% (<i>R,R</i>)-<b>4.16</b> 0.2% [(<i>S,S</i>)+(<i>R,S</i>)]-<b>4.16</b> 1.3% (<i>S,R</i>)-<b>4.16</b></p>
 <p>96.1% (<i>R,R</i>)-<b>4.16</b> 2.9% [(<i>S,S</i>)+(<i>R,S</i>)]-<b>4.16</b> 1.0% (<i>S,R</i>)-<b>4.16</b></p>	<div style="border: 1px solid black; padding: 10px; display: flex; justify-content: space-around; align-items: center;"> <div> <p>Mes =</p>  </div> <div> <p>Ant =</p>  </div> </div>		

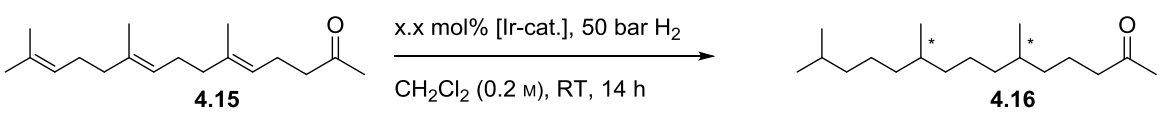
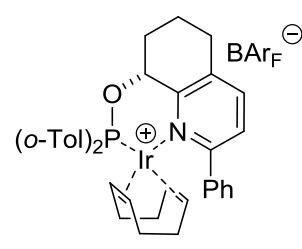
**Table 4.5:** Bicyclic pyridine-based catalyst with large aryl substituents in the hydrogenation of (*5E,9E*)-farnesylacetone (reaction conditions: 0.2 mmol substrate, 1.0 mol% catalyst loading, 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), RT, 14 h). Complete conversion was obtained for all entries.

Next, the influence of larger aryl substituents at the 2-position of the pyridine moiety was studied. Complexes of this type had already emerged as efficient catalysts in the hydrogenation of (*2E,6E*)-farnesol (see chapter 2).<sup>[90]</sup> Also in the hydrogenation of (*5E,9E*)-farnesylacetone **4.15** these catalysts were capable of achieving higher selectivities compared to their analogs bearing the phenyl substituent. Especially the anthracenyl derivatives provided extraordinarily high selectivities. In this case, 97.4% and 98.5% of the major stereoisomer were obtained with catalyst **4.52** and **4.53** respectively (table 4.5).

## 4.3.1.3 Catalyst loading

Although catalysts **4.52** and **4.53** showed superior selectivity than catalyst **4.45**, the optimization of the reaction conditions was conducted with catalyst **4.45**. Given that the synthesis of this complex is better investigated and thus can be achieved more efficiently. Moreover, since the price of the catalyst plays an important role towards a possible application, the use of catalyst **4.45** is preferred over catalysts **4.52** and **4.53**. In addition, due to their sterically more congested environment around the metal center, in general lower reactivity was observed for these iridium complexes when compared to catalyst **4.45** (see chapter 2 and 3).

**Table 4.6:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**): influence of catalyst loading.

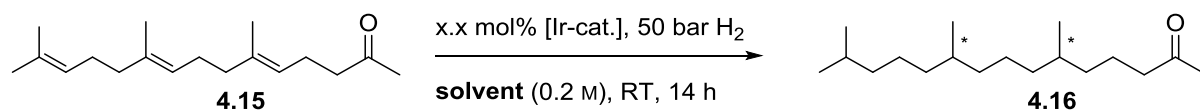
				
Entry	Cat	Cat loading [mol%]	<b>4.16</b> [%] <sup>[a]</sup>	Stereoisomers [%] <sup>[b]</sup>
1		1.0	>99	96.6 ( <i>S,S</i> ) 1.2 [( <i>R,R</i> )+( <i>S,R</i> )] 2.2 ( <i>R,S</i> )
2		0.5	>99	96.7 ( <i>S,S</i> ) 0.8 [( <i>R,R</i> )+( <i>S,R</i> )] 2.5 ( <i>R,S</i> )
3		0.2	>99	95.2 ( <i>S,S</i> ) 1.0 [( <i>R,R</i> )+( <i>S,R</i> )] 3.8 ( <i>R,S</i> )
4		0.1	28	n.d.

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by GC analysis after derivatization.

The systematic reduction of the catalyst loading revealed that at 0.2 mol% still complete reduction was obtained. However, a small erosion of stereoselectivity was observed at reduced catalyst loading (table 4.6).

## 4.3.2 Solvent screening

## 4.3.2.1 Screening of different solvents

**Table 4.7:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**): solvent screening.

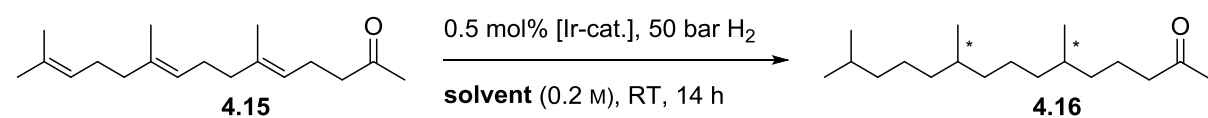
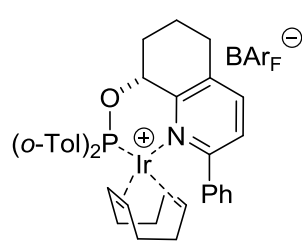
Entry	Cat	Cat loading [mol%]	Solvent	<b>4.16</b> [%] <sup>[a]</sup>	Stereoisomers [%] <sup>[b]</sup>
1		0.2	propylene carbonate	1	n.d.
2		0.2	chlorobenzene	1	n.d.
3		0.2	toluene	1	n.d.
4		0.5	CF <sub>3</sub> CH <sub>2</sub> OH	>99	97.8 ( <i>S,S</i> ) 0.9 [( <i>R,R</i> )+( <i>S,R</i> )] 1.3 ( <i>R,S</i> )
5		0.2	CF <sub>3</sub> CH <sub>2</sub> OH	47	n.d.
6		1	(CF <sub>3</sub> ) <sub>2</sub> CHOH	>99	98.1 ( <i>S,S</i> ) 0.7 [( <i>R,R</i> )+( <i>S,R</i> )] 1.2 ( <i>R,S</i> )
7		0.1	(CF <sub>3</sub> ) <sub>2</sub> CHOH	76	n.d.
8		1	C <sub>6</sub> F <sub>6</sub>	>99	97.1 ( <i>S,S</i> ) 0.9 [( <i>R,R</i> )+( <i>S,R</i> )] 2.0 ( <i>R,S</i> )
9		0.2	C <sub>6</sub> F <sub>6</sub>	18	n.d.
10		1	fluorobenzene	>99	95.9 ( <i>S,S</i> ) 1.1 [( <i>R,R</i> )+( <i>S,R</i> )] 3.0 ( <i>R,S</i> )
11		0.2	fluorobenzene	3	n.d.
12		1.0	trifluorotoluene	>99	95.7 ( <i>S,S</i> ) 1.2 [( <i>R,R</i> )+( <i>S,R</i> )] 3.1 ( <i>R,S</i> )
13		0.2	trifluorotoluene	1	n.d.

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by GC analysis after derivatization.

In the next step the applicability of different solvents was tested. Solvents such as propylene carbonate, chlorobenzene and toluene, which have been successfully applied in the

hydrogenation of other substrates, showed significantly reduced conversion compared to  $\text{CH}_2\text{Cl}_2$  at 0.2 mol% catalyst loading. Fluorinated solvents such as  $\text{CF}_3\text{CH}_2\text{OH}$  (TFE) or  $(\text{CF}_3)_2\text{CHOH}$  (HFIP) showed full conversion with up to 98.1% selectivity for the major stereoisomer (table 4.7, entry 6). HFIP showed even higher TONs than  $\text{CH}_2\text{Cl}_2$  (table 4.7, entry 7 vs. table 4.1, entry 4). Although these fluorinated solvents showed superior selectivity, their application to an industrial process poses a significant challenge due to their high price. For this reason only TFE can be considered as potential solvent and therefore different mixtures of  $\text{CH}_2\text{Cl}_2$  and TFE were tested for their applicability in the hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**) with the goal to achieve the selectivity provided by TFE and the TONs obtained in  $\text{CH}_2\text{Cl}_2$ .

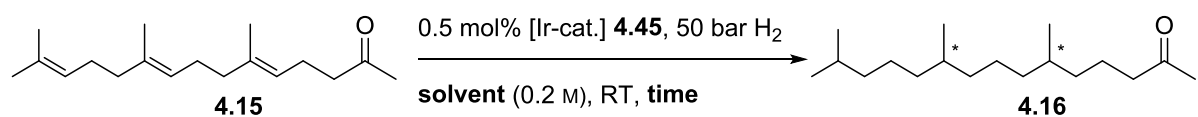
**Table 4.8:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**): screening of solvent mixtures.

				
Entry	Cat	Solvent	Ratio	<b>4.16</b> [%] <sup>[a]</sup>
1		$\text{CH}_2\text{Cl}_2:\text{CF}_3\text{CH}_2\text{OH}$	99:1	91
2		$\text{CH}_2\text{Cl}_2:\text{CF}_3\text{CH}_2\text{OH}$	19:1	99
3		$\text{CH}_2\text{Cl}_2:\text{CF}_3\text{CH}_2\text{OH}$	7:1	98
4		$\text{CH}_2\text{Cl}_2:\text{CF}_3\text{CH}_2\text{OH}$	3:1	>99

[a] Determined by GC analysis on an achiral stationary phase.

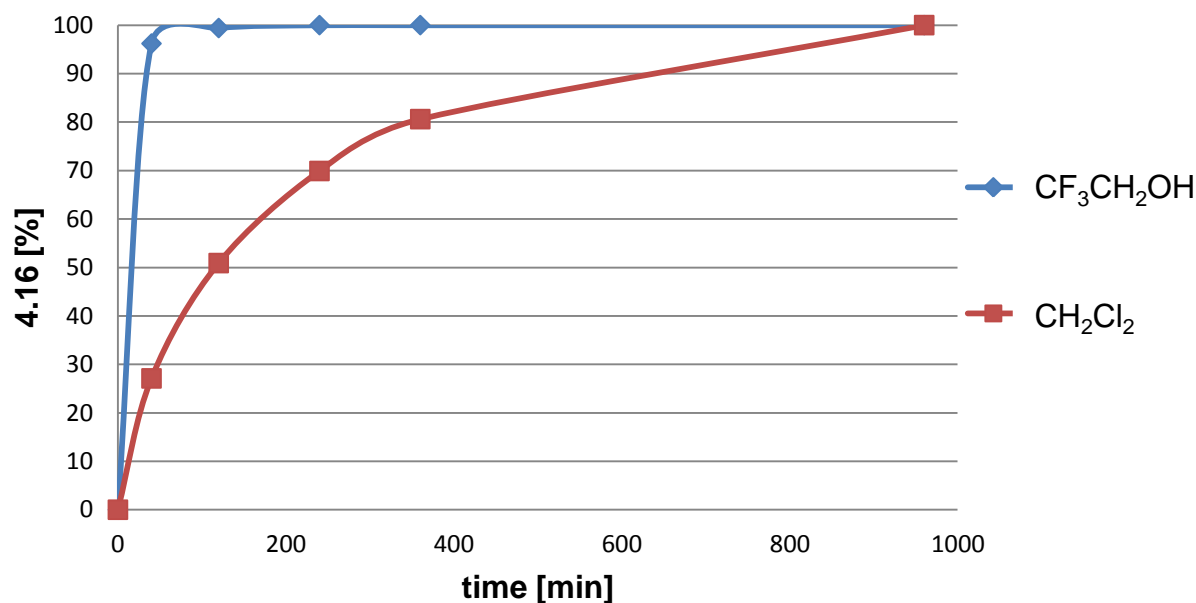
The combination of  $\text{CH}_2\text{Cl}_2$  and TFE proved inefficient in the hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**). Full conversion was only observed at a ratio of 3:1 with the use 0.5 mol% catalyst loading (table 4.8, entry 4). However, at this catalyst loading both pure  $\text{CH}_2\text{Cl}_2$  and TFE previously showed complete conversion to 6,10,14-trimethylpentadecan-2-one (**4.16**). Due to the significantly reduced reactivity, the selectivity of the reactions conducted in the solvent mixtures was not determined.

## 4.3.3 Kinetic studies

**Table 4.9:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**): kinetic study.

Entry	Solvent	Time [min]	<b>4.16</b> [%] <sup>[a]</sup>	Entry	Solvent	Time [min]	<b>4.16</b> [%] <sup>[a]</sup>
1	CH <sub>2</sub> Cl <sub>2</sub>	40	27	5	CF <sub>3</sub> CH <sub>2</sub> OH	40	96
2	CH <sub>2</sub> Cl <sub>2</sub>	120	51	6	CF <sub>3</sub> CH <sub>2</sub> OH	120	>99
3	CH <sub>2</sub> Cl <sub>2</sub>	240	70	7	CF <sub>3</sub> CH <sub>2</sub> OH	240	>99
4	CH <sub>2</sub> Cl <sub>2</sub>	360	81	8	CF <sub>3</sub> CH <sub>2</sub> OH	360	>99
5	CH <sub>2</sub> Cl <sub>2</sub>	960	>99	10	CF <sub>3</sub> CH <sub>2</sub> OH	960	>99

[a] Determined by GC analysis on an achiral stationary phase.

**Figure 4.2:** Plot of the formation of **4.16** vs. time.

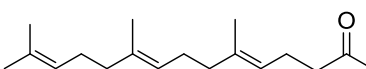
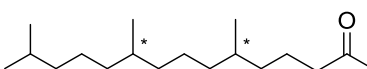
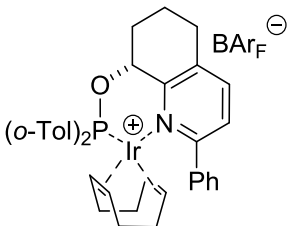
To explore the differences between TFE and CH<sub>2</sub>Cl<sub>2</sub>, the reactivity of catalyst **4.45** in these two solvents was studied. After evaluating of the data obtained, it became clear that TFE provides a much faster reaction rate compared to CH<sub>2</sub>Cl<sub>2</sub> (table 4.9 and figure 4.2).



## 4.4 Tris(perfluorophenyl)borane as additive in the hydrogenation

Conversion is an important parameter for the application of Ir-catalysts to the hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**). To further improve this parameter the influence of tris(perfluorophenyl)borane (**4.55**) and its properties as additive to quench nucleophilic impurities, like water, in the reaction mixture was investigated. The reaction of this borane with a nucleophile should result in the formation of negatively charged boron species with similar properties to the BAr<sub>F</sub> counterion.

**Table 4.10:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**) in the presence of tris(perfluorophenyl)borane (**4.55**).

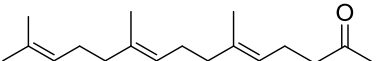
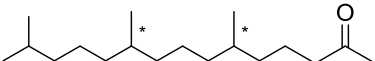
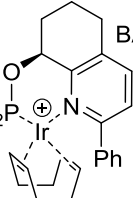
<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p><b>4.15</b></p> </div> <div style="text-align: center;"> <p>x.x mol% <b>additive</b>              0.08 mol% [Ir-cat.], 50 bar H<sub>2</sub>              CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), RT, 14 h</p> </div> <div style="text-align: center;">  <p><b>4.16</b></p> </div> </div>				
Entry	[Ir-cat.]	Additive	Additive [mol%]	<b>4.16</b> [%] <sup>[a]</sup>
1		none	0	<1 <sup>[b]</sup>
2		(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> B	1	2
3		(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> B	2.5	29
4		(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> B	5	51

[a] Determined by GC analysis on an achiral stationary phase; [b] Partially hydrogenated compounds were observed.

Tris(perfluorophenyl)borane (**4.55**) showed excellent behavior to increase the TONs of the catalyst. In fact, in the presence of 5 mol% of tris(perfluorophenyl)borane the formation of 51% of the fully reduced farnesylacetone was observed. In contrast, the control experiment without additive showed only traces of the fully reduced product **4.16** (table 4.10). One could assume that further increasing the amount of tris(perfluorophenyl)borane could result in full conversion, but its high price limits the amount of additive that can be employed for this reaction.

To further study the applicability of tris(perfluorophenyl)borane as additive, the selectivity of the hydrogenation in the presence of this species was determined (scheme 4.11).

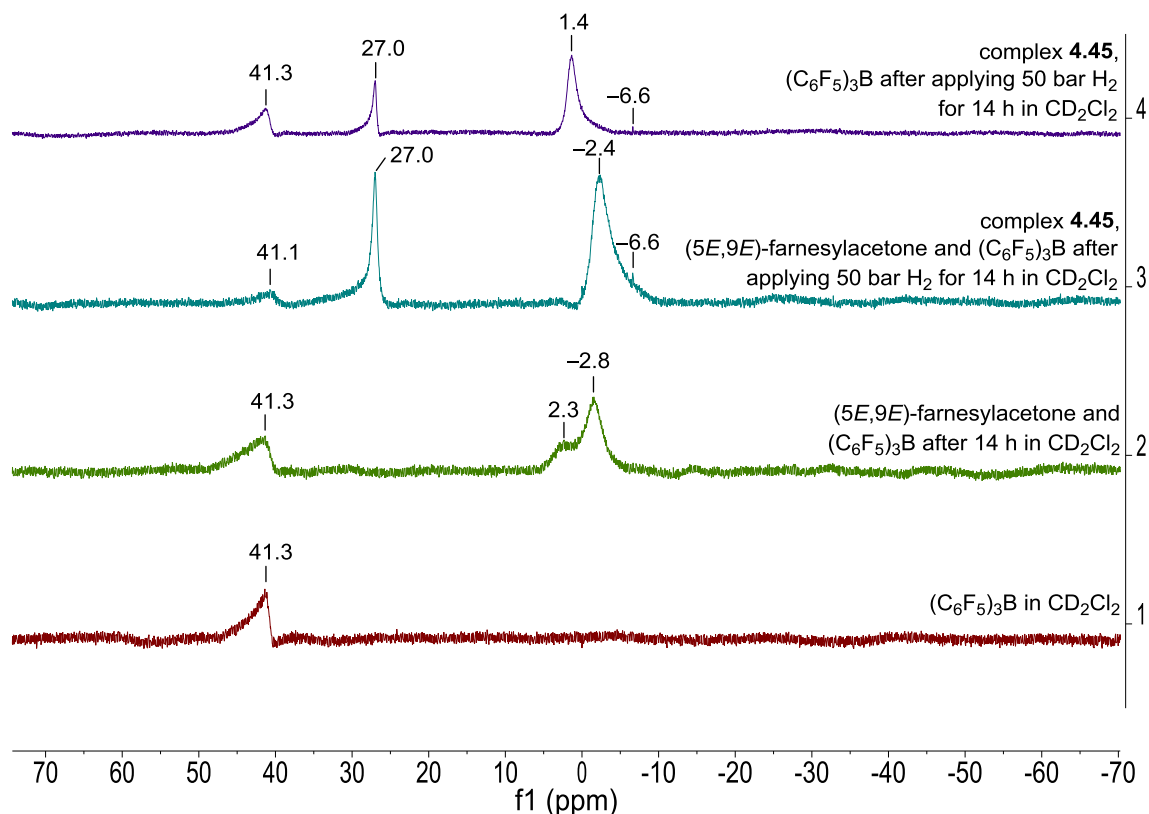
**Table 4.11:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**) in the presence of (C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>B.

 <p style="text-align: center;"><b>4.15</b></p>	5.0 mol% (C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> B 0.5 mol% [Ir-cat.], 50 bar H <sub>2</sub> <hr/> CH <sub>2</sub> Cl <sub>2</sub> (0.2 M), RT, 14 h	 <p style="text-align: center;"><b>4.16</b></p>
with additive		without additive
2.8% (6 <i>S</i> ,10 <i>S</i> )- <b>4.16</b> , 4.1% (6 <i>S</i> ,10 <i>R</i> )- <b>4.16</b> 0.0% (6 <i>R</i> ,10 <i>S</i> )- <b>4.16</b> , 93.1% (6 <i>R</i> ,10 <i>R</i> )- <b>4.16</b>		2.8% (6 <i>S</i> ,10 <i>S</i> )- <b>4.16</b> , 1.5% (6 <i>S</i> ,10 <i>R</i> )- <b>4.16</b> 0.0% (6 <i>R</i> ,10 <i>S</i> )- <b>4.16</b> , 95.7% (6 <i>R</i> ,10 <i>R</i> )- <b>4.16</b>

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM.

The addition of tris(perfluorophenyl)borane (**4.55**) led to lower selectivities. However, still 93% of the main stereoisomer was formed compared to 95.7% for the reaction without the additive (table 4.11). Interestingly, the erosion of selectivity took place exclusively at C6. This stereogenic center is generated by the hydrogenation of the double bond, which is in the closest proximity to the ketone and at this position the strongest interaction between the substrate and the Lewis base is assumed.

To analyze the role of tris(perfluorophenyl)borane, <sup>11</sup>B NMR-experiments were carried out to better understand how the borane **4.55** interacts with the other species in the reaction mixture. The following samples were prepared under inert conditions inside a glove box and subsequently analyzed by NMR spectroscopy (figure 4.3): 1. tris(perfluorophenyl)borane in CD<sub>2</sub>Cl<sub>2</sub> (red); 2. tris(perfluorophenyl)borane, (5*E*,9*E*)-farnesylacetone (20 eq.) in CD<sub>2</sub>Cl<sub>2</sub> (green); 3. tris(perfluorophenyl)borane, (5*E*,9*E*)-farnesylacetone (20 eq.), iridium catalyst **4.45** (0.016 eq.) in CD<sub>2</sub>Cl<sub>2</sub> (blue); 4. tris(perfluorophenyl)borane, iridium catalyst **4.45** (0.016 eq.), 50 bar H<sub>2</sub> then 1 bar N<sub>2</sub> in CD<sub>2</sub>Cl<sub>2</sub> (purple).



**Figure 4.3:**  $^{11}\text{B}$  NMR spectra of different reaction mixtures using  $(\text{C}_6\text{F}_5)_3\text{B}$  as additive.

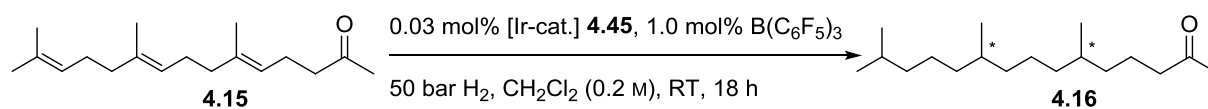
The  $^{11}\text{B}$  NMR spectrum, of tris(perfluorophenyl)borane showed a broad singlet at 41.3 ppm (red). The addition of  $(5E,9E)$ -farnesylacetone (**4.15**) resulted in the formation of probably two new species showing two broad signals at 2.3 and -2.8 ppm (green). These values of chemical shifts are typical of tetravalent ate complexes between the borane and the ketone or other nucleophilic impurities, such as water. After addition of the catalyst, the reaction mixture was stirred for 14 h under 50 bar hydrogen pressure. A new signal at 27.0 ppm showed the formation of a new borane species (blue). This signal also appeared in the absence of the substrate **4.15** (purple) and therefore might belong to a species which is generated from a catalytic reaction of the iridium complex with tris(perfluorophenyl)borane. The formation of this species deriving from a stoichiometric reaction of tris(perfluorophenyl)borane with the iridium complex can be excluded based on the ratio of borane to catalyst (62.5:1) and the comparable high quantity of this newly formed peak. The nature of this species could not be identified. The  $^{11}\text{B}$ -signal for the counterion of the catalyst appeared as small spike at -6.6 ppm.

The main conclusions drawn from this and additional experiments on the effect of tris(perfluorophenyl)borane are:

1.  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and GC-MS showed neither polymerization product nor formation of the corresponding alcohol which might occur as a result of the activation of the ketone by the borane species.
2. The fact that in each  $^{11}\text{B}$  NMR spectra free tris(perfluorophenyl)borane was observed, indicates that tris(perfluorophenyl)borane is probably not irreversible bond to the ketone and therefore not entirely quenched in the course of the reaction.
3. No borohydride was observed which could be generated by hydride exchange with the activated catalyst. An additional hydride is necessary for the formation of the inactive trinuclear iridium hydride complex observed for PHOX complexes and is assumed as the main deactivation pathway for these catalysts.<sup>[25]</sup>

In addition, the hydrogenation conducted for the NMR experiment showed complete conversion applying identical reaction conditions as described before (5.0 mol% boron species, 0.08 mol% catalyst loading, figure 4.3 (blue)). In the previous experiment 51% conversion to the fully reduced product **4.16** was observed. The main difference between these experiments is that in the case of full conversion the reaction mixture was stirred longer before applying hydrogen pressure.

Therefore several experiments were conducted to disclose the optimal order of addition and the influence on the different reaction components. The different reaction mixtures were stirred for 24 h at room temperature under  $\text{N}_2$  atmosphere in the glove box. Then 50 bar hydrogen pressure were applied. The following reactions were carried out at 0.03 mol% catalyst loading to further reduce the amount of catalyst.

**Table 4.12:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**) in the presence of tris(perfluorophenyl)borane (**4.55**).

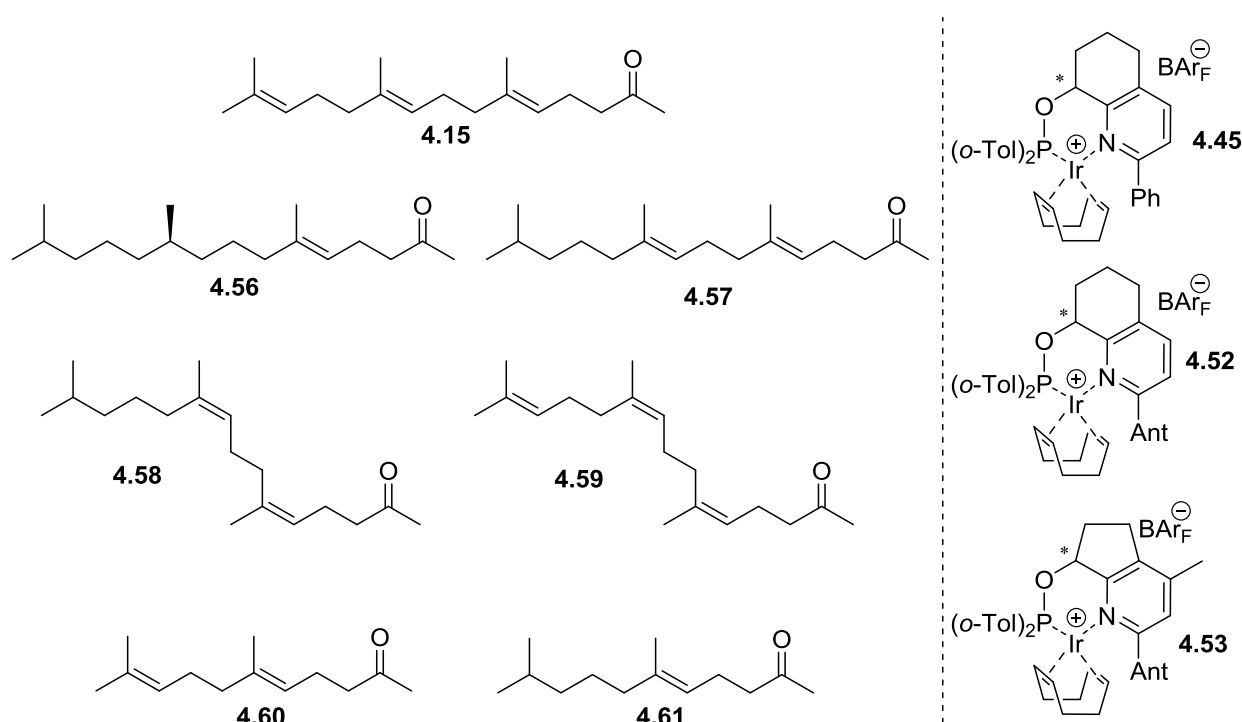
		B [%] <sup>[a]</sup>	TON <sup>[a,b]</sup>
<b>4.15</b> + [Ir-cat.] + B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub>	1) 24 h	<1 <sup>[c]</sup>	~770
	2) 50 bar H <sub>2</sub> , 18 h		
<b>4.15</b> + B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub>	1) 24 h	2	~2600
	2) [Ir-cat.], 50 bar H <sub>2</sub> , 18 h		
[Ir-cat.] + B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub>	1) 24 h	<1 <sup>[c]</sup>	~580
	2) <b>4.15</b> , 50 bar H <sub>2</sub> , 18 h		
<b>4.15</b>	1) 24 h	<1 <sup>[c]</sup>	~72
	2) [Ir-cat.], (C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> B, 50 bar H <sub>2</sub> , 18 h		

[a] Determined by GC analysis on an achiral stationary phase; [b] TONs were calculated based on the number of C=C bonds reduced per catalyst molecule; [c] Partially hydrogenated compounds were observed.

The way how tris(perfluorophenyl)borane was applied as additive in the hydrogenation of (5*E*,9*E*)-farnesylacetone had a significant influence on the TONs (table 4.12). If the substrate was stirred for 24 h in the presence of tris(perfluorophenyl)borane followed by hydrogenation, the highest TON value was achieved. In contrast, if the borane was added directly prior to the hydrogenation significantly lower TONs were obtained.

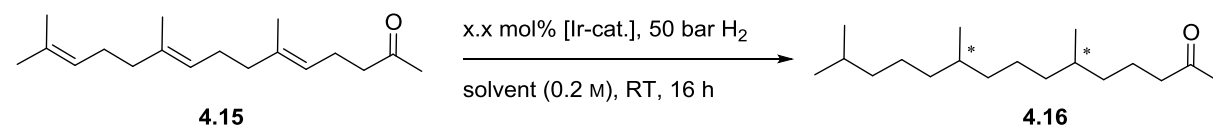
## 4.5 Hydrogenation of $\gamma,\delta$ -unsaturated ketones

To further demonstrate the applicability of iridium-based catalysts in the hydrogenation of intermediates in the synthesis of the tocopherol side chain, several  $\gamma,\delta$ -unsaturated ketones were tested using the best catalysts identified from the previous screening (figure 4.4). Additionally, the determination of the selectivity was in this case performed by DSM. This method allowed for the assignment of all four stereoisomers. The entries in the following tables are arranged by selectivity in decreasing order.



**Figure 4.4:**  $\gamma,\delta$ -Unsaturated ketones screened using selected iridium catalysts.

4.5.1 Hydrogenations of (5*E*,9*E*)-farnesylacetone**Table 4.13:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**).

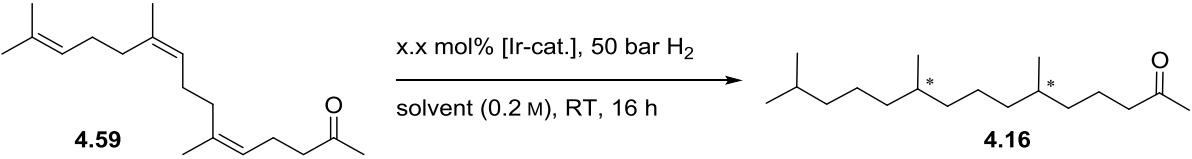
										
Entry	Cat/ (config)	Solvent	Cat loading [mol%]	<b>4.16</b> [%] <sup>[a]</sup>	(6 <i>R</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>R</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>	<i>dr</i>
1	<b>4.52</b> /( <i>R</i> )	TFE	1.0	>99	0.8	0.00	0.1	99.1	>99	124:1
2	<b>4.52</b> /( <i>R</i> )	HFIP	1.0	>99	0.7	0.4	0.0	98.9	>99	94:1
3	<b>4.53</b> /( <i>S</i> )	TFE	1.0	>99	0.5	1.6	97.9	0.0	>99	48:1
4	<b>4.45</b> /( <i>R</i> )	HFIP	1.0	>99	1.7	1.1	0.00	97.2	>99	34:1
5	<b>4.45</b> /( <i>R</i> )	TFE	1.0	>99	1.7	1.4	0.0	96.9	>99	31:1
6	<b>4.45</b> /( <i>R</i> )	TFE	0.5	>99	1.8	1.6	0.0	96.6	>99	29:1
7	<b>4.53</b> /( <i>S</i> )	HFIP	1.0	>99	2.0	1.6	96.4	0.0	>99	27:1
8	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	3.0	1.4	0.0	95.7	>99	22:1
9	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	0.5	>99	2.8	1.5	0.00	95.7	>99	22:1

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM; [c] Enantiomeric excess of the major stereoisomer.

Catalyst **4.52** and TFE emerged as the most selective combination for the hydrogenation of (5*E*,9*E*)-farnesylacetone (**4.15**). In this case almost exclusively the desired stereoisomer was formed (99.1%) with a *dr* of 124:1 (table 4.13, entry 1). For catalyst **4.45** slightly higher selectivity was obtained in HFIP compared to TFE (entries 4 and 5). In addition, a slight erosion of selectivity was observed when reducing the catalyst loading for catalyst **4.45** (entry 6).

## 4.5.2 Hydrogenation of (5Z,9Z)-farnesylacetone

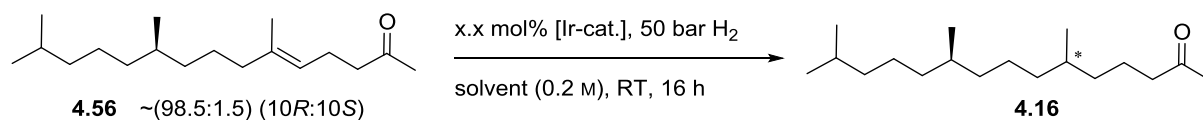
**Table 4.14:** Hydrogenation of (5Z,9Z)-farnesylacetone (**4.59**).

										
Entry	Cat/ (config)	Solvent	Cat loading [mol%]	<b>4.16</b> [%] <sup>[a]</sup>	(6 <i>R</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>R</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>	<i>dr</i>
1	<b>4.52</b> /( <i>R</i> )	TFE	1.0	>99	1.8	3.1	95.1	0.0	>99	19:1
2	<b>4.45</b> /( <i>R</i> )	TFE	1.0	>99	2.2	3.4	94.4	0.0	>99	17:1
3	<b>4.45</b> /( <i>R</i> )	TFE	0.5	>99	2.4	3.3	94.3	0.0	>99	17:1
4	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	2.4	3.4	94.2	0.0	>99	16:1
5	<b>4.52</b>	CH <sub>2</sub> Cl <sub>2</sub>	1.0	70	n.d.	n.d.	n.d.	n.d.	--	--
6	<b>4.45</b>	CH <sub>2</sub> Cl <sub>2</sub>	0.5	41	n.d.	n.d.	n.d.	n.d.	--	--
7	<b>4.53</b>	CH <sub>2</sub> Cl <sub>2</sub>	1.0	7	n.d.	n.d.	n.d.	n.d.	--	--

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DMS; [c] Enantiomeric excess of the major stereoisomer.

The hydrogenation of (5Z,9Z)-farnesylacetone showed a different reactivity compared to (5E,9E)-farnesylacetone. In the case of the opposite geometry of the C=C double bonds TFE proved to be superior to CH<sub>2</sub>Cl<sub>2</sub> in terms of selectivity and also reactivity. The best selectivity was obtained with catalyst **4.52** in TFE, affording the desired stereoisomer in 95.1% (table 4.14, entry 1). In general, the selectivities and reactivities were lower than those obtained with (5E,9E)-farnesylacetone (**4.15**).

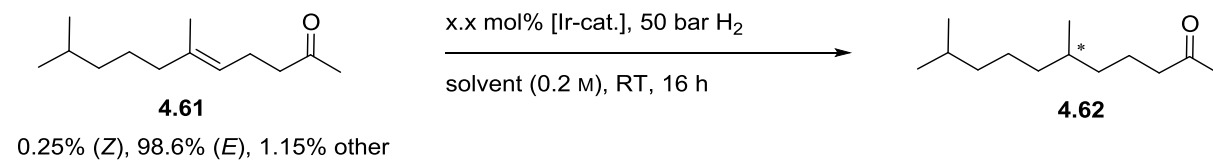


4.5.3 Hydrogenation of (5*E*,10*R*)-tetrahydrofarnesylacetone**Table 4.15:** Hydrogenation of (5*E*,10*R*)-tetrahydrofarnesylacetone (**4.56**).

Entry	Cat/ (config)	Solvent	Cat loading [mol%]	Conv. [%] <sup>[a]</sup>	(6 <i>R</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>R</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	ratio (C6)
1	<b>4.45</b> /( <i>R</i> )	TFE	0.5	>99	0.0	97.1	1.5	1.4	98.5:1.5
2	<b>4.45</b> /( <i>S</i> )	TFE	1.0	>99	1.3	1.7	97.0	0.0	98.3:1.7
3	<b>4.52</b> /( <i>R</i> )	TFE	1.0	>99	0.0	97.0	0.9	2.1	99.1:0.9
4	<b>4.52</b> /( <i>S</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	1.3	1.8	96.9	0.0	98.2:1.8
5	<b>4.45</b> /( <i>R</i> )	TFE	1.0	>99	0.0	96.1	1.9	2.0	98.1:1.9
6	<b>4.45</b> /( <i>S</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	1.6	2.5	96.0	0.0	97.5:2.5
7	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	0.5	>99	0.0	95.8	2.7	1.5	97.3:2.7
8	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	0.0	95.6	2.9	1.5	97.1:2.9

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM.

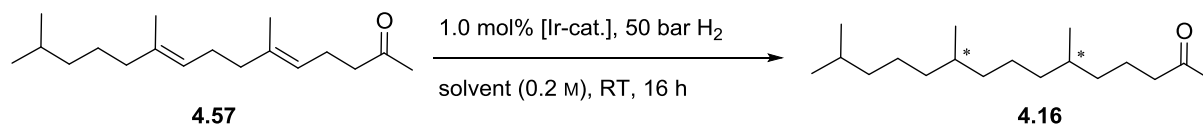
A similar order of selectivity at C6 was observed in the hydrogenation (5*E*,10*R*)-tetrahydrofarnesylacetone compared with (5*E*,9*E*)-farnesylacetone. TFE in combination with catalyst **4.52** provided a ratio of 99.1:0.9 on C6 (table 4.15, entry 3). Furthermore, no significant influence of the stereogenic center at C10 on the selectivity of the hydrogenation was observed (entry 1 vs. 2 and entry 6 vs. 8).

4.5.4 Hydrogenation (5*E*)-dihydrogeranylacetone**Table 4.16:** Hydrogenation of (5*E*)-dihydrogeranylacetone (**4.61**).

Entry	Cat/ (config)	Solvent	Cat loading [mol%]	Conv. [%] <sup>[a]</sup>	(6 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> ) [%] <sup>[b]</sup>	ee [%]
1	<b>4.52</b> /( <i>R</i> )	TFE	1.0	>99	0.7	99.3	99 ( <i>S</i> )
2	<b>4.53</b> /( <i>S</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	98.9	1.1	98 ( <i>R</i> )
3	<b>4.45</b> /( <i>R</i> )	TFE	1.0	>99	98.6	1.4	97 ( <i>S</i> )
4	<b>4.52</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	1.4	98.6	97 ( <i>S</i> )
5	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	2.3	97.7	95 ( <i>S</i> )
6	<b>4.45</b> /( <i>R</i> )	TFE	0.5	>99	3.6	96.4	93 ( <i>S</i> )
7	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	0.5	>99	6.7	93.2	87 ( <i>S</i> )

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM.

(5*E*)-Dihydrogeranylacetone (**4.61**) is one of the side chain precursors which would allow for a stepwise introduction of the stereogenic centers. In this series excellent selectivities were obtained, especially if the presence of the (*Z*)-isomer (0.25%) in the starting material is taken into account. As for the previous substrates, the combination of catalyst **4.52** and TFE afforded the highest enantiomeric excess with 99% (table 4.16, entry 1). Catalyst **4.53** emerged as slightly superior to catalyst **4.52** when the reaction was performed in CH<sub>2</sub>Cl<sub>2</sub> (entry 2).

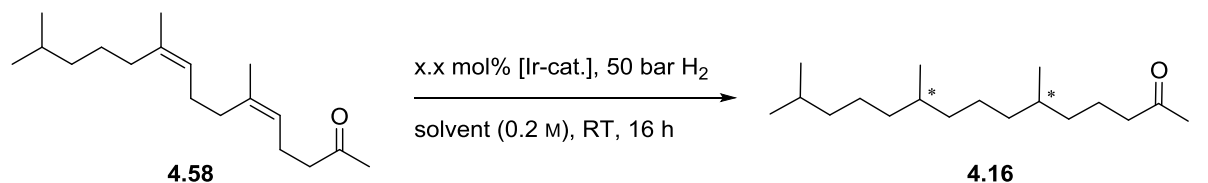
4.5.5 Hydrogenation of (5*E*,9*E*)-dihydrofarnesylacetone**Table 4.17:** Hydrogenation of (5*E*,9*E*)-dihydrofarnesylacetone (**4.57**).

Entry	Cat/ (config)	Solvent	<b>4.16</b> [%] <sup>[a]</sup>	(6 <i>R</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>R</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>	<i>dr</i>
1	<b>4.52</b> /( <i>R</i> )	TFE	>99	0.0	4.4	0.0	95.6	>99	22:1
2	<b>4.52</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	>99	1.0	4.4	0.0	94.6	>99	18:1
3	<b>4.53</b> /( <i>S</i> )	CH <sub>2</sub> Cl <sub>2</sub>	>99	4.6	0.9	94.5	0.0	>99	17:1
4	<b>4.45</b> /( <i>R</i> )	TFE	>99	1.1	5.5	0.0	93.4	>99	14:1
5	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	>99	2.3	5.5	0.0	92.2	>99	12:1

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM; [c] Enantiomeric excess of the major stereoisomer.

In the hydrogenation of (5*E*,9*E*)-dihydrofarnesylacetone (**4.57**) in general lower selectivities were observed compared to (5*E*,9*E*)-farnesylacetone (**4.15**). Catalyst **4.52** showed the best result in TFE with 95.6% selectivity for the major stereoisomer. Catalysts **4.52** and **4.53** performed almost similarly in CH<sub>2</sub>Cl<sub>2</sub> (table 4.17, entry 2 and 3).

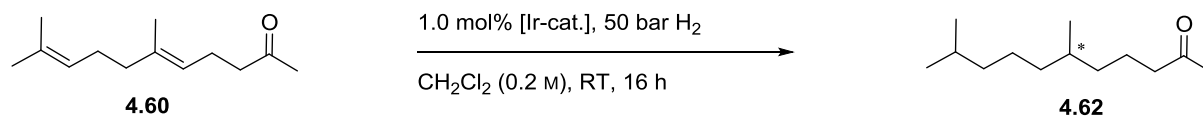
## 4.5.6 Hydrogenation of (5Z,9Z)-dihydrofarnesylacetone

**Table 4.18:** Hydrogenation of (5Z,9Z)-dihydrofarnesylacetone (**4.58**).

Entry	Cat/ (config)	Solvent	Cat loading [mol%]	<b>4.16</b> [%] <sup>[a]</sup>	(6 <i>R</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>R</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>	<i>dr</i>
1	<b>4.52</b> /( <i>R</i> )	TFE	1.0	>99	1.3	1.6	97.2	0.00	>99	35:1
2	<b>4.53</b> /( <i>S</i> )	TFE	1.0	>99	1.6	1.3	0.00	97.1	>99	33:1
3	<b>4.52</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	1.2	2.2	96.6	0.00	>99	28:1
4	<b>4.53</b> /( <i>S</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	2.2	1.3	0.0	96.5	>99	28:1
5	<b>4.45</b> /( <i>R</i> )	TFE	0.5	>99	1.7	2.0	96.3	0.0	>99	26:1
6	<b>4.45</b> /( <i>R</i> )	TFE	1.0	>99	1.7	2.0	96.3	0.0	>99	26:1
7	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	1.8	2.2	96.0	0.0	>99	24:1
8	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	0.5	>99	1.8	2.4	95.8	0.0	>99	23:1
9	<b>4.45</b> /( <i>R</i> )	TFE	0.2	81	n.d.	n.d.	n.d.	n.d.	--	--
10	<b>4.45</b> /( <i>R</i> )	CH <sub>2</sub> Cl <sub>2</sub>	0.2	39	n.d.	n.d.	n.d.	n.d.	--	--

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined DSM; [c] Enantiomeric excess of the major stereoisomer.

Comparing the hydrogenation of (5Z,9Z)-dihydrofarnesylacetone **4.58** and (5Z,9Z)-farnesylacetone **4.59**, almost identical values were obtained. Catalyst **4.52** in TFE emerged as the most selective combination with 97.2% for the desired stereoisomer (table 4.18, entry 1). In addition, higher conversions to the fully reduced substrate could be obtained by the use of the partially saturated substrate dihydrofarnesylacetone **4.58** (table 4.18, entry 8 vs. table 4.14 entry, 6).

4.5.7 Hydrogenation of (5*E*)-geranylacetone**Table 4.19:** Hydrogenation of (5*E*)-geranylacetone (**4.60**).

Entry	Cat/ (config.)	<b>4.62</b> [%] <sup>[a]</sup>	( <i>S</i> ) [%] <sup>[b]</sup>	( <i>R</i> ) [%] <sup>[b]</sup>
1		>99	>98%	<2%
2		>99	<2%	>98%

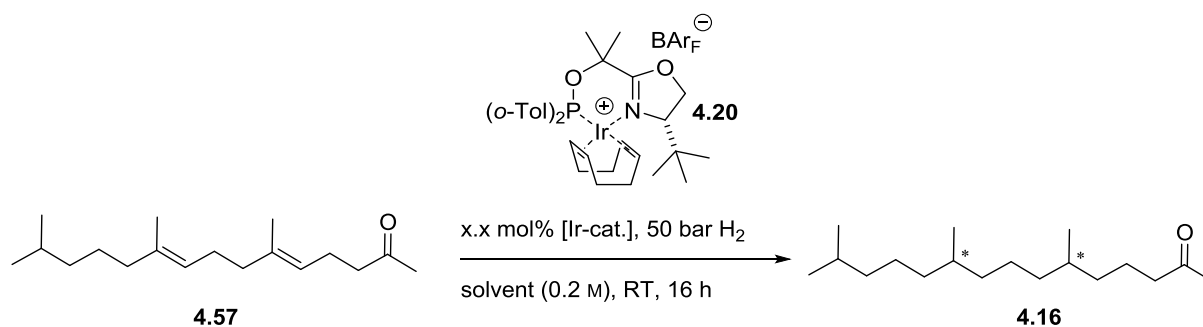
[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM.

In the hydrogenation of (5*E*)-geranylacetone (**4.60**), both catalysts tested provided excellent selectivity and full conversion using 1.0 mol% catalyst loading in CH<sub>2</sub>Cl<sub>2</sub> (table 4.19).

## 4.6 Hydrogenation of $\gamma,\delta$ -unsaturated ketones using a di-*o*-tolylphosphinite-*tert*-butyl-simplePHOX-based catalyst

In the course of the screening, the simplePHOX-based catalyst **4.20** achieved excellent selectivity at the C6 position in the hydrogenation of (5*E*,9*E*)-dihydrofarnesylacetone (**4.57**) (table 4.20, entry 1). This catalyst is significantly easier to synthesize than the catalyst scaffold applied before. Therefore, additional experiments were conducted to test the applicability of a stepwise hydrogenation/chain elongation/hydrogenation sequence by the use of this catalyst.

**Table 4.20:** Hydrogenations of (5*E*,9*E*)-dihydrofarnesylacetone (**4.57**) using di-*o*-tolylphosphinit-*tert*-butyl-simplePHOX (**4.20**).

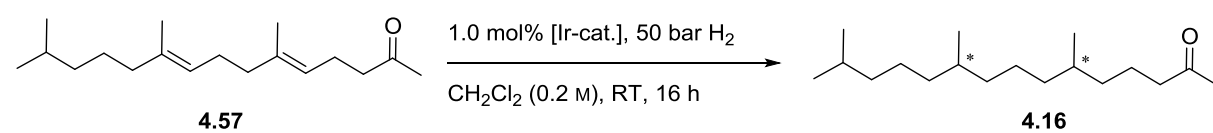
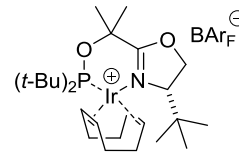
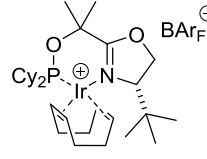
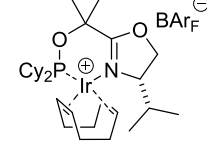
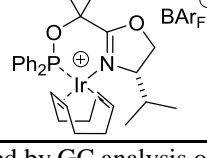


Entry	Solvent	Cat loading [mol%]	<b>4.16</b> [%] <sup>[a]</sup>	(6 <i>R</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>R</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	selectivity (C6)	<i>dr</i>
1	CH <sub>2</sub> Cl <sub>2</sub>	1.0	>99	1.2	26.2	0.4	72.2	59:1	2.6:1
2	TFE	1.0	>99	1.3	36.8	0.7	61.2	49:1	1.6:1
3	TFE	0.5	83	n.d.	n.d.	n.d.	n.d.	--	--
4	CH <sub>2</sub> Cl <sub>2</sub>	0.5	8	n.d.	n.d.	n.d.	n.d.	--	--
5	TFE	0.2	4	n.d.	n.d.	n.d.	n.d.	--	--
6	CH <sub>2</sub> Cl <sub>2</sub>	0.2	<1 <sup>[c]</sup>	n.d.	n.d.	n.d.	n.d.	--	--

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM, [c] Partially hydrogenated compounds were observed.

The hydrogenations with the simplePHOX-based catalyst **4.20** showed inverse behavior compared to the pyridine-based catalyst investigated before. In CH<sub>2</sub>Cl<sub>2</sub> a higher selectivity and in TFE higher conversion were observed. In general, the reactivity was lower, leading to incomplete conversion already at 0.5 mol% catalyst loading (table 4.20, entry 4). Taking into account that in this hydrogenation only one double bond is reduced, the catalyst is more than three times less reactive. Therefore derivatives of this catalyst were tested in order to find a more active analog.

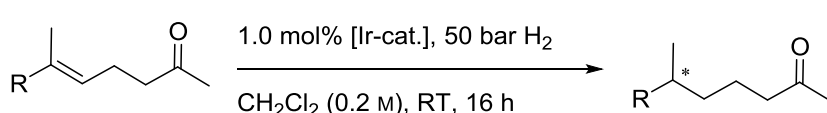
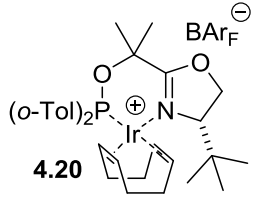
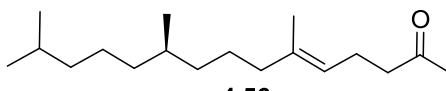
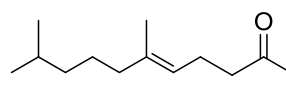
**Table 4.21:** Hydrogenations of (5*E*,9*E*)-dihydrofarnesylacetone (**4.56**) using simplePHOX derivatives.

								
Entry	Cat	<b>4.16</b> [%] <sup>[a]</sup>	(6 <i>R</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>R</i> , 10 <i>R</i> ) [%] <sup>[b]</sup>	(6 <i>S</i> , 10 <i>S</i> ) [%] <sup>[b]</sup>	selectivity (C6)	<i>dr</i>
1		>99	14.5	35.9	12.1	37.5	2.8:1	1:1
2		83	n.d.	n.d.	n.d.	n.d.	--	--
3		>99	15.1	34.6	17.3	33.0	2.1:1	1:1
4		45	n.d.	n.d.	n.d.	n.d.	--	--

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM.

All catalysts of this series showed either incomplete conversion at 1.0 mol% catalyst loading or poor selectivity at C6 (table 4.21). As a result, catalyst **4.20** remains the most promising candidate for a stepwise approach to introduce the stereogenic centers in the tocopherol side chain.

**Table 4.22:** Substrates involved in a stepwise approach for the introduction of the stereogenic centers.

		
 <p><b>4.56</b></p> <p>~(98.5:1.5) (10<i>R</i>:10<i>S</i>)</p> <p>conv. = &gt;99%<sup>[a]</sup></p> <p>(6<i>R</i>,10<i>S</i>) [%]<sup>[b]</sup> = 0.0%; (6<i>S</i>,10<i>R</i>) [%]<sup>[b]</sup> = 96.8%</p> <p>(6<i>R</i>,10<i>R</i>) [%]<sup>[b]</sup> = 1.8%; (6<i>S</i>,10<i>S</i>) [%]<sup>[b]</sup> = 1.4%</p> <p>ratio (C6) = 98.2:1.8</p>	 <p><b>4.61</b></p> <p>conv. = &gt;99%<sup>[a]</sup></p> <p>(6<i>R</i>) [%]<sup>[b]</sup> = 17.6%; (6<i>S</i>) [%]<sup>[b]</sup> = 82.4%</p> <p>ee = 65%</p>	

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by DSM.

Complex **4.20** emerged as an efficient catalyst to introduce the second stereogenic center in the hydrogenation of (5*E*,10*R*)-tetrahydrofarnesylacetone (**4.56**). A ratio of 98.2:1.8 at C6 was observed (table 4.22). Surprisingly, the hydrogenation of (5*E*)-dihydrogeranylacetone (**4.61**) showed significantly lower selectivity when compared to (5*E*,10*R*)-tetrahydrofarnesylacetone. With respect to the results obtained applying the pyridine based catalyst in which similar selectivity at C6 was observed for the hydrogenation of all farnesyl and geranyl derivatives, this significant drop of selectivity for (5*E*)-dihydrogeranylacetone was rather unexpected.

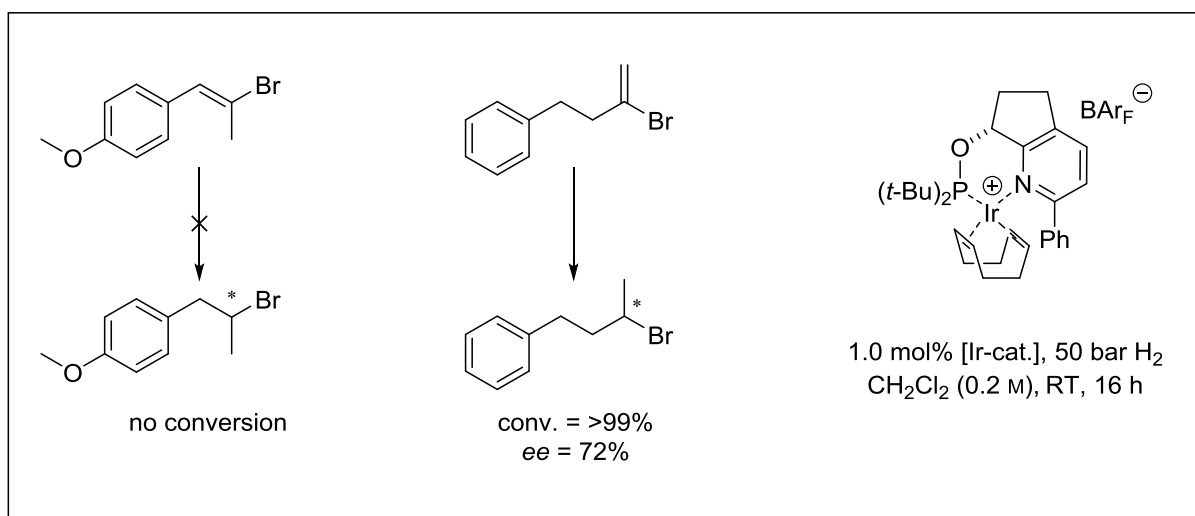


## 4.7 Conclusion

In summary, iridium-based N,P ligand complexes emerged as efficient catalysts for the hydrogenation of tocopherol side chain precursors. Especially, the hydrogenation of (5*E*,9*E*)-farnesylacetone, from an industrial perspective the most relevant precursor, resulted in the formation of 99.1% of the desired stereoisomer. In addition, good reactivity was observed in the hydrogenation of this substrate. The reaction reached complete conversion to the saturated ketone using only 0.2 mol% catalyst loading. This is especially remarkable considering that three double bonds are reduced in one single step. If and to what extent this methodology can be applied to the stereoselective synthesis of (*R,R,R*)- $\alpha$ -tocopherol depends on many factors. In that context, many parameters such as the efficiency of the introduction of the last stereogenic center, the extent to which the reactivity can be increased on a larger scale and the price development for *all-rac*- $\alpha$ -tocopherol and in particular (*R,R,R*)- $\alpha$ -tocopherol have to be taken into account. However, with the encouraging results obtained from this study in hands, further investigations towards the industrial stereoselective synthesis of (*R,R,R*)- $\alpha$ -tocopherol seem to be promising.

## Chapter 5

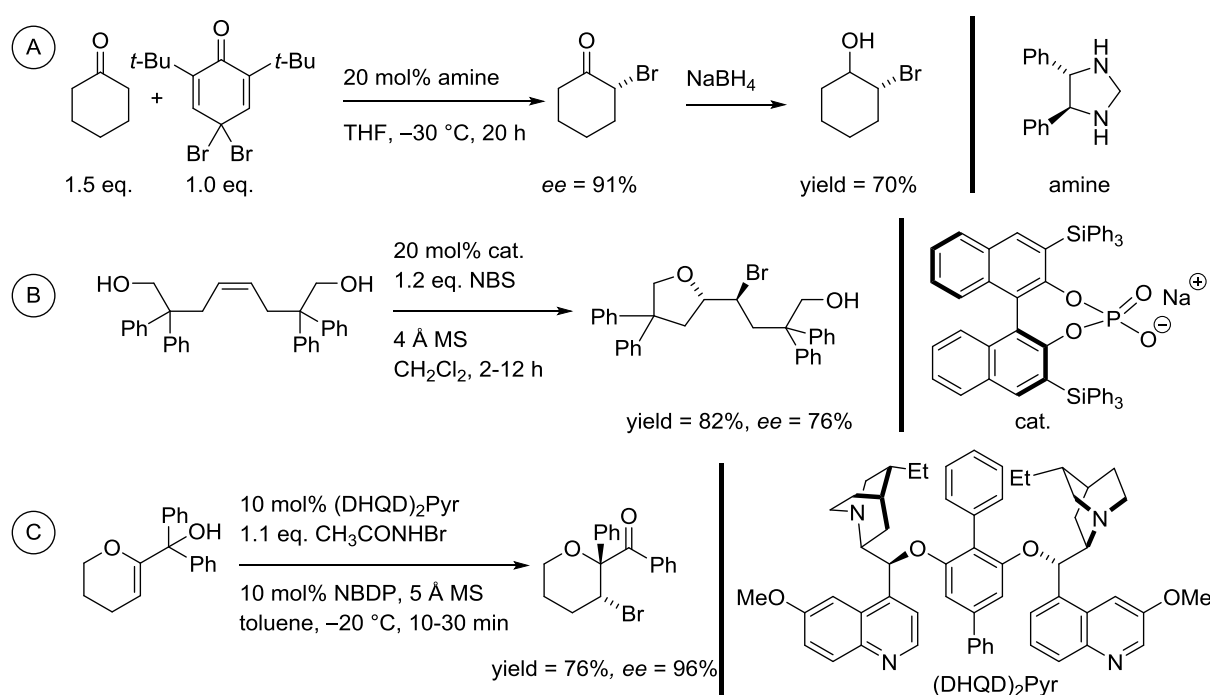
### Vinyl Bromides as Substrates for the Asymmetric Hydrogenation with Iridium N,P Ligand Complexes



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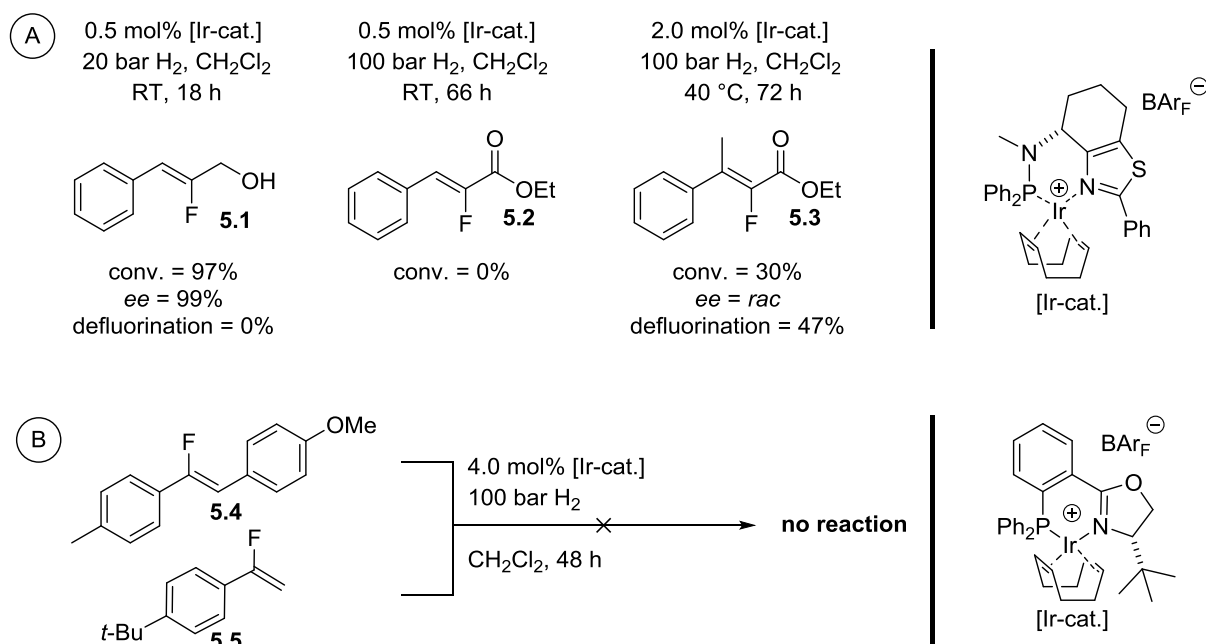
## 5.1 Introduction

The synthesis of bromide containing molecules by hydrobromination of alkenes is one of the reactions which is felt to be in the toolbox of every organic chemist ever since. The bromide itself is a group which allows for many synthetic transformations<sup>[91]</sup> and when attached to a stereogenic center, stereospecific S<sub>N</sub>2 displacement may be used to retain chirality, in order to generate a diversity of optically enriched products. In this context it is rather surprising, that methods to generate enantioenriched molecules with a bromide directly attached to the stereogenic center have not been extensively investigated or are limited in substrate scope. Catalytic methods which allow the introduction of a “bromonium-ion” to an  $\alpha$ -acidic position of compounds such as ketones or acid chlorides have been better explored and high enantioselectivities can be reached (scheme 5.1, A).<sup>[92]</sup> An alternative approach is the asymmetric bromination of olefins. This strategy can lead to high enantioselectivity but only for substrates containing an additional nucleophile which is capable to attack the bromonium-ion formed within the reaction to generate five or six-membered rings (scheme 5.1, B). In a few cases this strategy was successfully applied to substrates which are capable to trap the bromonium-ion by a rearrangement. Furthermore, for both methods predominantly only moderate yields were obtained (scheme 5.1, C).<sup>[93]</sup>



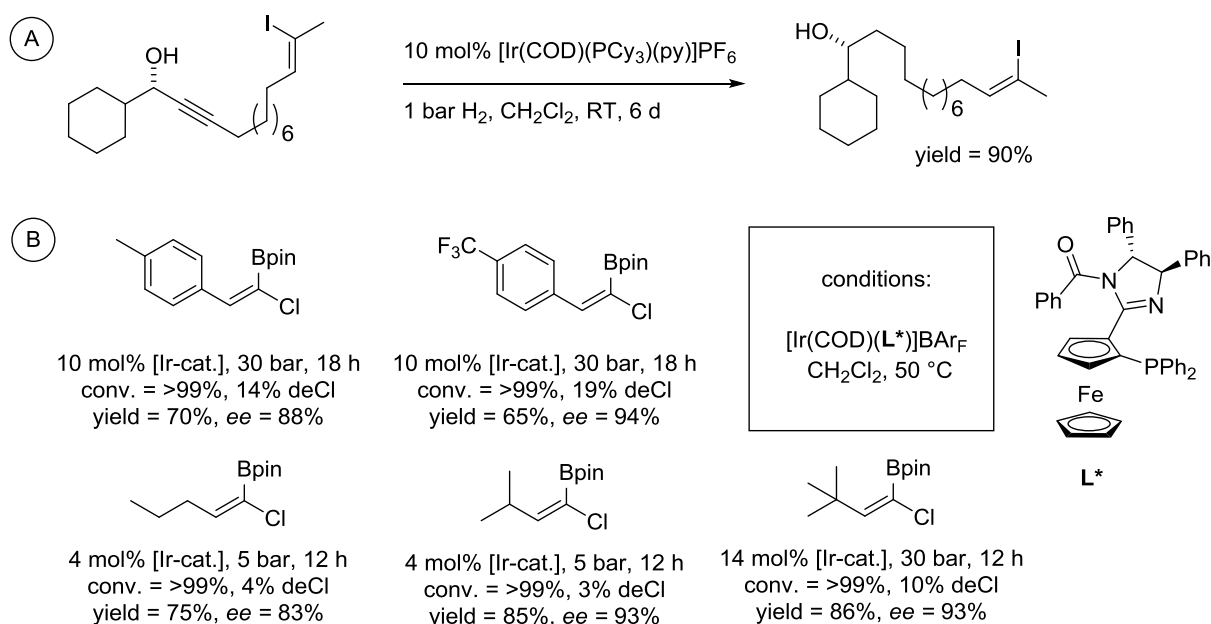
**Scheme 5.1:** Different approaches to synthesize enantiomerically enriched compounds containing a bromide at the stereogenic center.  $\alpha$ -Bromination,<sup>[94]</sup> A; Enantioselective haloetherification,<sup>[95]</sup> B; Organocatalytic asymmetric bromination/semipinacol rearrangement,<sup>[96]</sup> C.

There is no report demonstrating the application of iridium N,P ligand complexes in the hydrogenation of vinyl bromides up to date. However, vinyl fluorides and vinyl chlorides have been tested as substrates with varying degrees of success. Although these substrates differ from vinyl bromides, to a certain extent important conclusions can be drawn based on the results obtained in these reports. Andersson and co-workers published on the hydrogenation of vinyl fluorides (scheme 5.2, A). Excellent results were only obtained for substrate **5.1** containing an additional hydroxyl group. The fluoride substituted allylic alcohol **5.1** reacted with 97% conversion and 99% enantiomeric excess was obtained. Other substrates bearing an additional coordinating group showed inferior results.<sup>[97]</sup> In addition, the tetrasubstituted substrate **5.3** showed higher reactivity but significant amounts of defluorinated product was formed compared to the trisubstituted analog **5.2**, which showed no reactivity at all. These results show that this substrate class is highly structure dependent and even higher reactivity of tetra substituted substrates over trisubstituted ones can be observed. The hydrogenation of vinyl fluorides containing no additional functional group was investigated by Dr. David Woodmansee.<sup>[54a]</sup> In this study no reactivity was obtained by applying harsh reaction conditions with 4 mol% catalyst, 100 bar hydrogen pressure and 48 hours reaction time. Even for the terminal vinyl fluoride **5.5** no conversion to the desired product was observed (scheme 5.2, B).



**Scheme 5.2:** Hydrogenation of vinyl fluorides containing an additional functional group, A; and attempts to hydrogenate vinyl fluorides without an additional coordinating group, B.

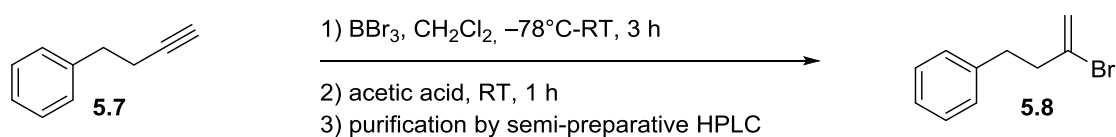
Parker and co-workers reported the hydrogenation of an alkyne by the use of Crabtree's catalyst. The vinyl iodide moiety in this molecule remained completely intact (scheme 5.3, A).<sup>[98]</sup> The most promising results in this field were obtained in the enantioselective hydrogenation of (1-chloro-1-alkenyl) boronic esters (scheme 5.3, B).<sup>[99]</sup> Although relatively high amounts of dechlorination was observed, the high enantioselectivity obtained with this method, makes it the most straightforward approach to synthesize these versatile chiral building blocks.



**Scheme 5.3:** Application of Crabtree's catalyst in the presence of a vinyl iodide, A; and the hydrogenation of (1-chloro-1-alkenyl) boronic esters by iridium N,P ligand complexes.

## 5.2 Hydrogenation of vinyl bromides

To start the evaluation of vinyl bromides as substrates for the asymmetric hydrogenation with iridium N,P ligand complexes, the terminal vinyl bromide **5.8** was synthesized *via* the addition of boron tribromide to 4-phenyl-1-butyne (**5.7**), which led to the corresponding 2-bromo-alkenylborane. This intermediate was subsequently hydrolyzed by acetic acid to afford (3-bromobut-3-en-1-yl)benzene (**5.8**) followed by purification on semi-preparative HPLC (scheme 5.4).



**Scheme 5.4:** Synthesis of (3-bromobut-3-en-1-yl)benzene (**5.8**).

In the hydrogenation of terminal substrates in general a significantly improved enantiomeric excess is reached when the reaction is conducted at 1 bar instead of 50 bar hydrogen pressure.<sup>[29a, 53d]</sup> However, at 1 bar hydrogen pressure only traces of the desired product **5.9** were observed (table 5.1). A maximum of 2% (3-bromobutyl)benzene (**5.9**) and 1% of the debrominated product butylbenzene (**5.10**), were observed for catalyst **5.11**. All other catalysts showed  $\leq 0.2\%$  formation of (3-bromobutyl)benzene (**5.9**).

**Table 5.1:** Catalyst screening for the hydrogenation of (3-bromobut-3-en-1-yl)benzene (**5.8**) at 1 bar  $\text{H}_2$ .

	<b>5.8</b>		<b>5.9</b>
	<b>5.10</b>		<b>5.10</b>
<hr/>			
	<b>5.11</b>		<b>5.12</b>
<b>5.9</b> = 2%		<b>5.9</b> = 0.2%	
<b>5.10</b> = 1%		<b>5.10</b> = 0.6%	
	<b>5.13</b>		<b>5.14</b>
<b>5.9</b> = 0.1%		<b>5.9</b> = 0.2%	
<b>5.10</b> = 0.5%		<b>5.10</b> = 0.8%	
	<b>5.15</b>		<b>5.16</b>
<b>5.9</b> = 0.1%		<b>5.9</b> = 0.2%	
<b>5.10</b> = 0.3%		<b>5.10</b> = 0.6%	

Conversion to **5.9** and **5.10** determined by GC on an achiral stationary phase.

Due to the low conversion obtained at 1 bar hydrogen pressure more forcing conditions with 50 bar hydrogen pressure and 16 hours reaction time were chosen. These conditions resulted in full conversion of the terminal vinyl bromide **5.8** and 72% *ee* was obtained, applying catalyst **5.11** (table 5.2). Although by the use of catalysts **5.11** and **5.18** full conversion was observed, all other catalysts of this series showed poor conversion, which therefore remained the major problem to be solved for this reaction.

**Table 5.2:** Catalyst screening for the hydrogenation of (3-bromobut-3-en-1-yl)benzene (**5.8**) at 50 bar H<sub>2</sub>.

<p><b>5.11</b></p> <p><b>5.9</b> = 99%, <i>ee</i> = 72% <b>5.10</b> = 1%</p>	<p><b>5.17</b></p> <p><b>5.9</b> = 7% <b>5.10</b> = 1%</p>	<p><b>5.18</b></p> <p><b>5.9</b> = 99%, <i>ee</i> = 2% <b>5.10</b> = 1%</p>
<p><b>5.19</b></p> <p><b>5.9</b> = 51% <b>5.10</b> = 2%</p>	<p><b>5.20</b></p> <p><b>5.9</b> = 77% <b>5.10</b> = 1%</p>	<p><b>5.21</b></p> <p><b>5.9</b> = 32% <b>5.10</b> = 1%</p>
<p><b>5.22</b></p> <p><b>5.9</b> = 0% <b>5.10</b> = 0.5%</p>	<p><b>5.23</b></p> <p><b>5.9</b> = 2% <b>5.10</b> = 0.5%</p>	<p><b>5.24</b></p> <p><b>5.9</b> = 1% <b>5.10</b> = 0%</p>

Conversion to **5.9** and **5.10** determined by GC on an achiral stationary phase. Enantiomeric excess was determined by HPLC on a chiral stationary phase.

Next, different solvents were screened (table 5.3). Both THF and CF<sub>3</sub>CH<sub>2</sub>OH showed lower conversion compared to CH<sub>2</sub>Cl<sub>2</sub>.

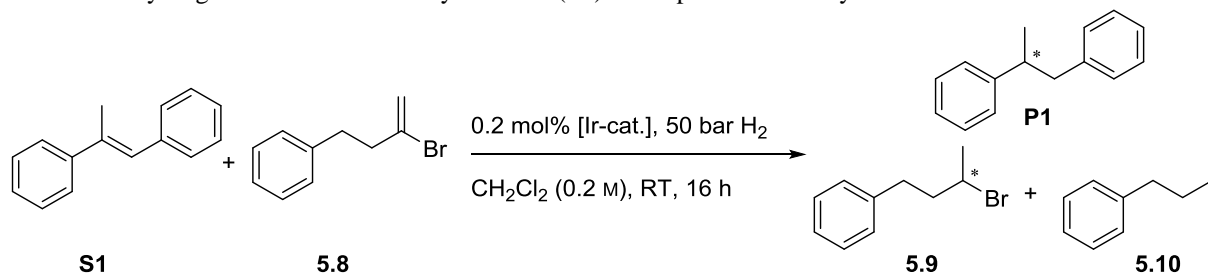
**Table 5.3:** Screened solvents in the hydrogenation of (3-bromobut-3-en-1-yl)benzene (**5.8**).

<b>5.8</b>			<b>5.9</b>		<b>5.10</b>
Entry	Cat.	Solvent	<b>5.9</b> [%] <sup>[a]</sup>	<i>ee</i> ( <b>5.9</b> ) [%] <sup>[b]</sup>	<b>5.10</b> [%] <sup>[a]</sup>
1		CH <sub>2</sub> Cl <sub>2</sub>	99	72	1
2		THF	48	n.d.	2
3		CF <sub>3</sub> CH <sub>2</sub> OH	97	60	2

[a] Conversion to **5.9** and **5.10** determined by GC on an achiral stationary phase; [b] Enantiomeric excess determined by HPLC on a chiral stationary phase.

The origin of the low reactivity of vinyl bromides in the asymmetric hydrogenation with iridium-based catalysts can be manifold. The double bond character with an additional halogen is significantly reduced compared to unfunctionalized olefins.<sup>[100]</sup> On the other hand, the sigma C–Br bond is significantly shortened to 1.86 Å in vinyl bromide compared to 1.91 Å in CH<sub>3</sub>Br.<sup>[101]</sup> Furthermore, the metal could insert into the C–Br which might result in debromination or catalyst decomposition. To get a vague idea on these effects we performed the hydrogenation of the trisubstituted olefin **S1** in the presence of vinyl bromide **5.8** (table 5.4). In the absence of the vinyl bromide **5.8**, depending on the catalyst used, *trans*-methylstilbene (**S1**) was converted in 51% or 14% conversion to compound **P1** (entries 1 and 3). By the addition of 0.3 eq. of vinyl bromide **5.8** the conversion of the trisubstituted olefin **S1** remained below 1%. However the vinyl bromide **5.8** was converted with 42% when catalyst **5.11** was used (entry 2). Based on these experiments it can be assumed that the problem is not that the substrates are inert towards reaction with the catalysts, but that an undesired deactivation of the catalyst occurs upon reaction between the iridium complex and vinyl bromide **5.8**. Thus it can be speculated that a bromide might be liberated in the course of the reaction, which could result in a counterion exchange resulting in deactivation of the catalyst.

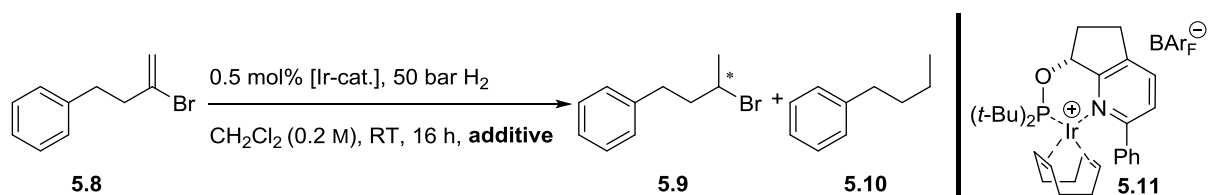


**Table 5.4:** Hydrogenation of *trans*-methyl stilbene (**S1**) in the presence of vinyl bromide **5.8**.

Entry	Cat.	5.8 [eq.]	Conv. of S1 [%] <sup>[a]</sup>	Conv. of 5.8 [%] <sup>[a]</sup>	5.10 [%]
1		--	51	--	--
2		0.3	0.5	42	0
3		--	14	--	--
4		0.3	0	0	0

[a] Conversions determined by GC on an achiral stationary phase.

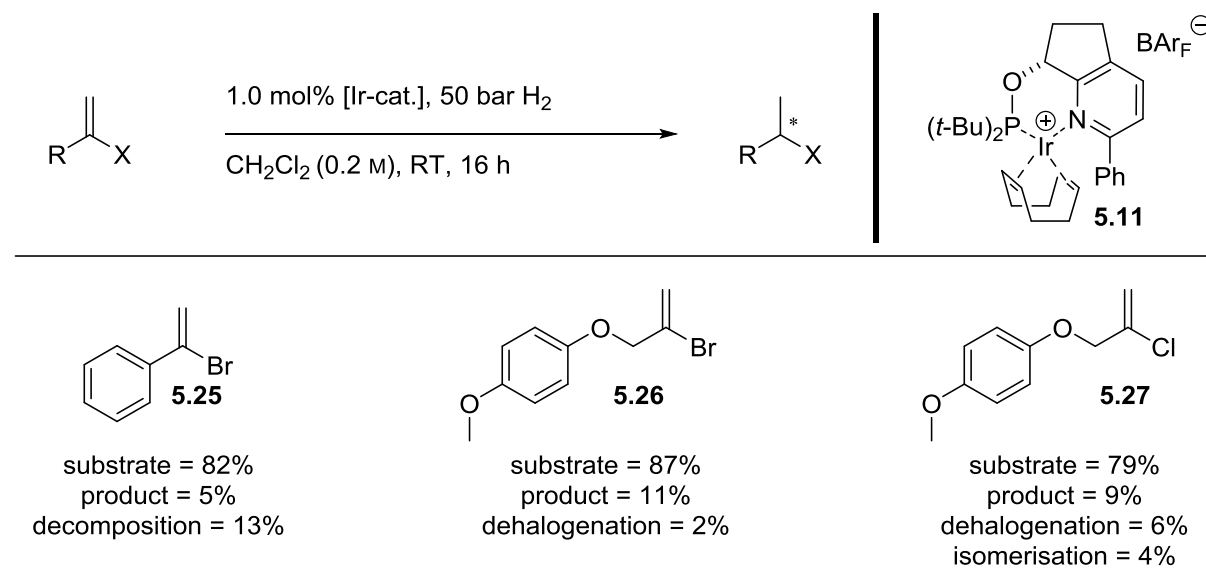
Therefore, different additives were tested, which potentially could act as scavenger and trap a bromide or perform an additional counterion exchange. In the absence of an additive 31% conversion was reached with 0.5 mol% catalyst loading (table 5.5). Indeed, by the addition of 0.1 eq. NaBAr<sub>F</sub> to the reaction mixture the conversion increased to 59% (entry 2). Other additives such as B(OCH(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub> resulted with 39% in only slightly higher conversions (entry 8). Although the addition of 0.1 eq. NaBAr<sub>F</sub> almost doubled the conversion, this increase was not enough to apply catalysts with other ligand classes tested in the previous screening (table 5.1 and 5.2). Also a further increase of the amount of NaBAr<sub>F</sub> used as additive, would lead to an expensive protocol due to the high price of NaBAr<sub>F</sub>.

**Table 5.5:** Screening of different additives in the hydrogenation of (3-bromobut-3-en-1-yl)benzene (**5.8**).

Entry	Additive	Eq.	<b>5.9</b> [%] <sup>[a]</sup>	<b>5.10</b> [%] <sup>[b]</sup>
1	--	--	31	1
2	NaBAr <sub>F</sub>	0.1	59	2
3	AgBAr <sub>F</sub>	0.1	42	7
4	AgSbF <sub>6</sub>	0.1	20	2
5	AgBF <sub>4</sub>	0.1	2	6
6	AgNO <sub>3</sub>	0.1	0	1
7	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub>	0.1	35	1
8	B(OCH(CH <sub>3</sub> ) <sub>2</sub> ) <sub>3</sub>	0.5	39	0.5
9	B(OCH <sub>3</sub> ) <sub>3</sub>	0.5	38	1
10	bis(pinacolato)diborane	0.1	33	1
11	tris(pentafluorophenyl)borane	0.1	22	0.5

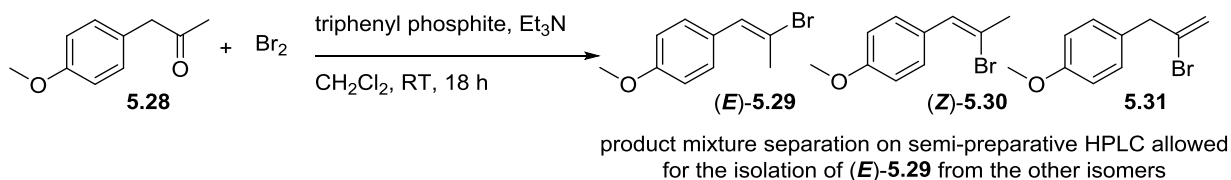
[a] Conversions determined by GC on an achiral stationary phase.

Next, different substrates were tested to gain a deeper insight on whether this low reactivity is substrate specific or a general characteristic of this substrate class. In this context, the substrates **5.25**, **5.26** and **5.27** were tested. (1-Bromovinyl)benzene (**5.25**) was commercially available and was purified by distillation, 1-((2-bromoallyl)oxy)-4-methoxybenzene (**5.26**) and 1-((2-chloroallyl)oxy)-4-methoxybenzene (**5.27**) were synthesized by substitution of 2,3-dichloroprop-1-ene or 2,3-dibromoprop-1-ene with 4-methoxyphenol. In the hydrogenation of these substrates significant amounts of dehalogenation, isomerization and decomposition were observed and no better results compared to the hydrogenation of (3-bromobut-3-en-1-yl)benzene (**5.8**) were obtained (scheme 5.5)



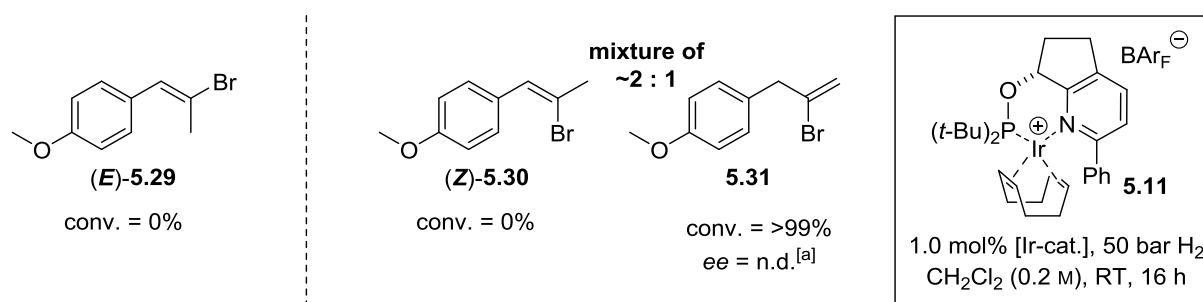
**Scheme 5.5:** Additional vinyl bromides tested in the asymmetric hydrogenation with iridium-based catalysts.

Next, trisubstituted vinyl bromides were investigated as substrates. Therefore, 1-(4-methoxyphenyl)propan-2-one (**5.28**) was treated with bromine and triphenyl phosphite to afford a mixture of three different vinyl bromides (scheme 5.6). Purification by semi-preparative HPLC resulted in the separation of (*E*)-isomer (*E*)-**5.29** and a 2:1 mixture of the (*Z*)-isomer (*Z*)-**5.30** and the vinyl bromide **5.31** containing a terminal C=C bond.



**Scheme 5.6:** Different isomers obtained from the reaction of 1-(4-methoxyphenyl)propan-2-one (**5.28**) with bromine and triphenyl phosphite.

In the hydrogenation of both trisubstituted vinyl bromides no consumption of the substrate was observed. Similar to the previously investigated vinyl bromide **5.8** with a terminal C=C bond, vinyl bromide **5.31** showed full conversion under the applied reaction conditions (scheme 5.7). No suitable conditions for the analysis of the enantiomeric excess of the product resulting from this reaction were found. However, based on the similar environment around the double bond compared to substrate **5.8** and the HPLC data which revealed partial separation of the two enantiomers similar results as for the terminal substrate **5.8** can be assumed.



**Scheme 5.7:** Hydrogenation of trisubstituted vinyl bromide (**E**)-**5.29** and of the mixture of trisubstituted vinyl bromide (**E**)-**5.30** and vinyl bromide **5.31** containing a terminal C=C bond. [a] Separation of the enantiomers was not possible.

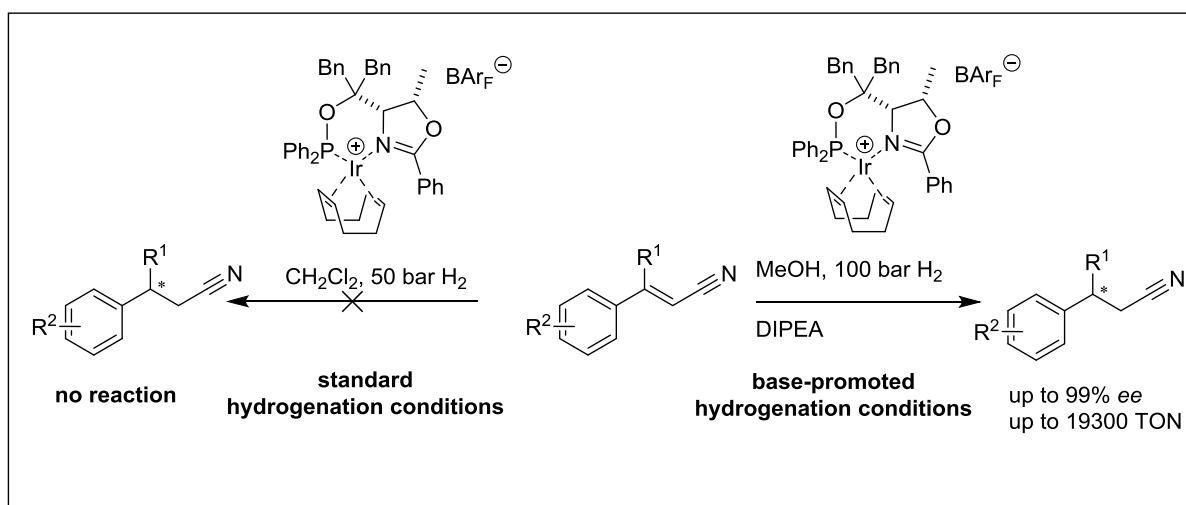
## 5.3 Conclusion

The reduction of vinyl bromides proved to be difficult using state-of-the-art iridium catalysts. At 1 bar hydrogen pressure which was previously demonstrated to be essential to achieve high enantioselectivities for terminal double bonds, only traces of the desired product were formed in the hydrogenation of the vinyl bromide **5.8**. Also at 50 bar hydrogen pressure only a few catalysts showed full conversion of the substrate and enantioselectivity of up to 72% were reached. The trisubstituted vinyl bromides were completely unreactive applying the most reactive catalyst identified in the previous screening.

As demonstrated for vinyl fluorides, an additional coordinating group might result in significant higher reactivity and would be a good starting point for further studies. On the other hand, this approach would considerably reduce the substrate scope.

# Chapter 6

## Asymmetric Hydrogenation of $\alpha,\beta$ -Unsaturated Nitriles with Base-Activated Iridium N,P Ligand Complexes



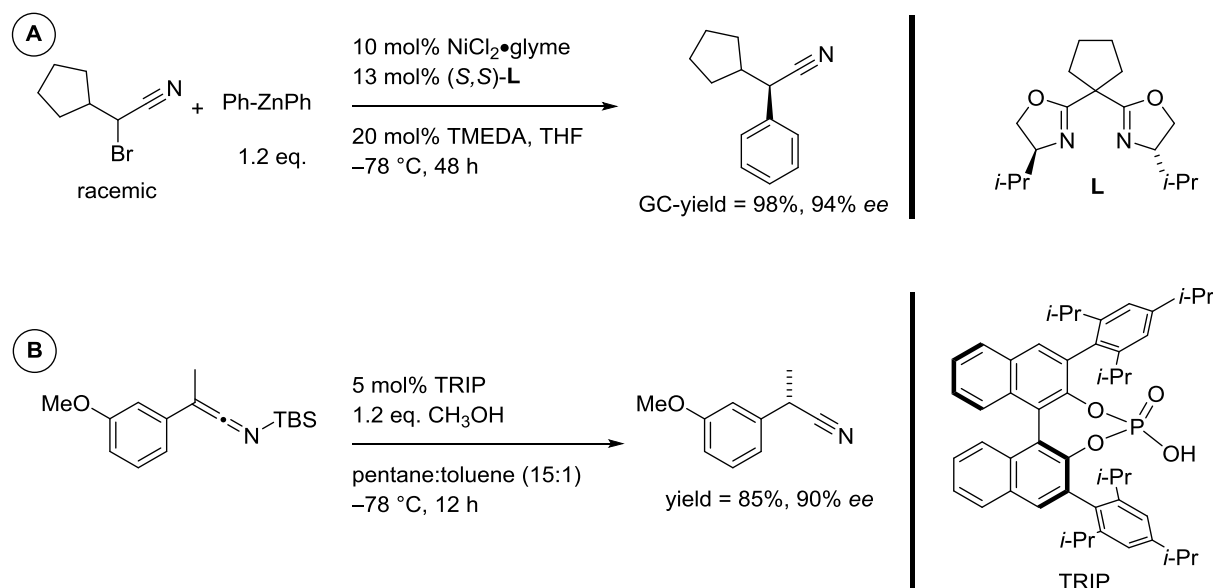
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## 6.1 Introduction

### 6.1.1 Synthesis of enantiomerically enriched nitriles

Most of the synthetic transformations carried out by organic chemists rely on functional groups. Among these functionalities, the cyano group plays an important role and is frequently used in many research areas. Nitriles are highly versatile building blocks in organic synthesis. They are commonly applied in cycloaddition reactions<sup>[102]</sup> and can be converted by simple manipulations into many different functional groups, such as carboxylic acids, ketones, aldehydes,  $\beta$ -keto esters, amines, imines or amides.<sup>[103]</sup> In addition, moieties bearing a stereogenic center at the  $\alpha$ - or  $\beta$ -position to a cyano group are frequently found in natural products.<sup>[104]</sup> Furthermore, the cyano group promotes adhesion of polymers to many substrates,<sup>[105]</sup> is known as pharmacophore in biologically active compounds<sup>[104b]</sup> and based on its weak  $\sigma$ -donor and  $\pi$ -acceptor ability, it is extensively used for the preparation of transition metal complexes.<sup>[106]</sup> The importance of nitriles, especially chiral ones, in organic chemistry prompts to the development of reliable, broadly applicable protocols for the enantioselective synthesis of molecules containing this specific group. However, synthetic protocols enabling the asymmetric synthesis of this compound class are limited. Asymmetric hydrocyanation of carbon-carbon double bonds provides the most obvious access to such molecules. Indeed, this transformation was studied by different research groups but only moderate selectivity is generally obtained.<sup>[107]</sup> Recently, Fu and co-workers published on a catalytic asymmetric synthesis of secondary nitriles *via* stereoconvergent Negishi arylation and alkenylation of racemic  $\alpha$ -bromonitriles (scheme 6.1, A).<sup>[108]</sup> Although *ees* up to 94% could be reached, high catalyst loadings, long reaction times and the limitation to aryl groups in  $\alpha$ -position are clear drawbacks of this method. An alternative approach was reported by List and co-workers on the catalytic asymmetric protonation of silyl ketene imines to generate  $\alpha$ -chiral nitriles (scheme 6.1, B).<sup>[109]</sup> With this protocol *ees* of around 90% were obtained, but only for silyl ketene imines bearing an aryl moiety directly attached to the double bond. Furthermore, the silyl ketene imines are synthesized from the racemic nitriles, by deprotonation and protection with a TBS-group. Therefore, this approach cannot be considered as a direct and atom economic way to generate enantiomerically enriched nitriles.



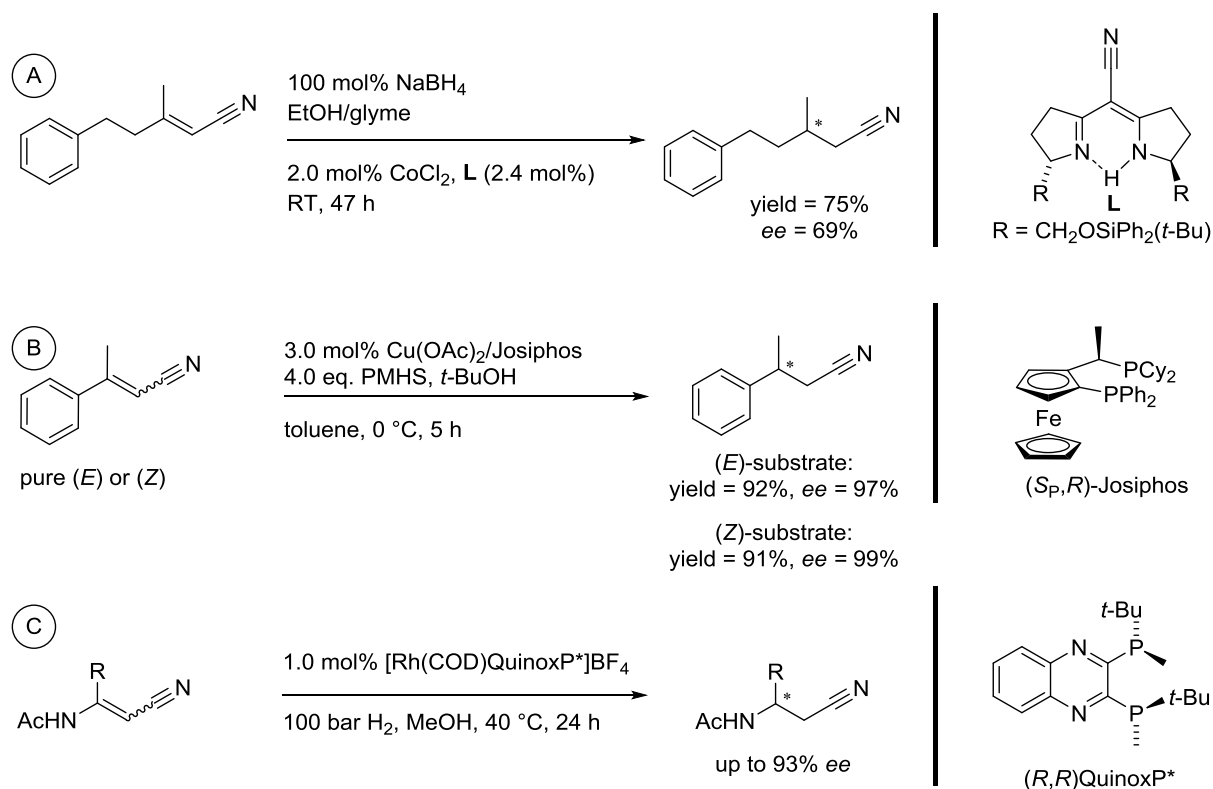
**Scheme 6.1:** State-of-the-art enantioselective synthesis of chiral nitriles.

### 6.1.2 Synthesis of enantiomerically enriched nitriles *via* asymmetric reductions

Besides the previously described methods, only a few protocols to generate enantiomerically enriched nitriles by asymmetric reductions of  $\alpha,\beta$ -unsaturated nitriles have been reported so far. Examples are the conjugate reduction with sodium borohydride catalyzed by semicorrin-cobalt complexes, copper-catalyzed reduction with hydrosiloxanes and rhodium-catalyzed asymmetric hydrogenation. In contrast to reductions of unsaturated esters and amides, which afforded *ee* values of >90%, the reduction of corresponding unsaturated nitriles with sodium borohydride catalyzed by semicorrin cobalt complexes led to moderate enantioselectivity (up to 69% *ee*) (scheme 6.2, A).<sup>[66]</sup> Albeit the chiral version of the Stryker's reagent,<sup>[67]</sup> based on Cu-Josiphos and polymethylhydrosiloxane (PMHS) as reducing agent, gave excellent enantioselectivities (of up to 99% *ee*), the relatively high catalyst loadings (3 mol%), a fourfold excess of PMHS, and strongly basic work-up conditions (aq. NaOH) are drawbacks of this method (scheme 6.2, B).<sup>[110]</sup> Although rhodium-catalyzed hydrogenation with hydrogen gas can provide high enantioselectivities, only unsaturated nitriles with an additional coordinating acetamido substituent or a carboxylate group at the C=C bond have been successfully applied, limiting considerably the chemical diversity accessible by this protocol (scheme 6.2, C).<sup>[111]</sup> In summary, despite the considerable synthetic value of enantioenriched nitriles and the efforts made within the last years, the number of methods enabling an efficient and broad access to this compound class is overall still limited. The goal



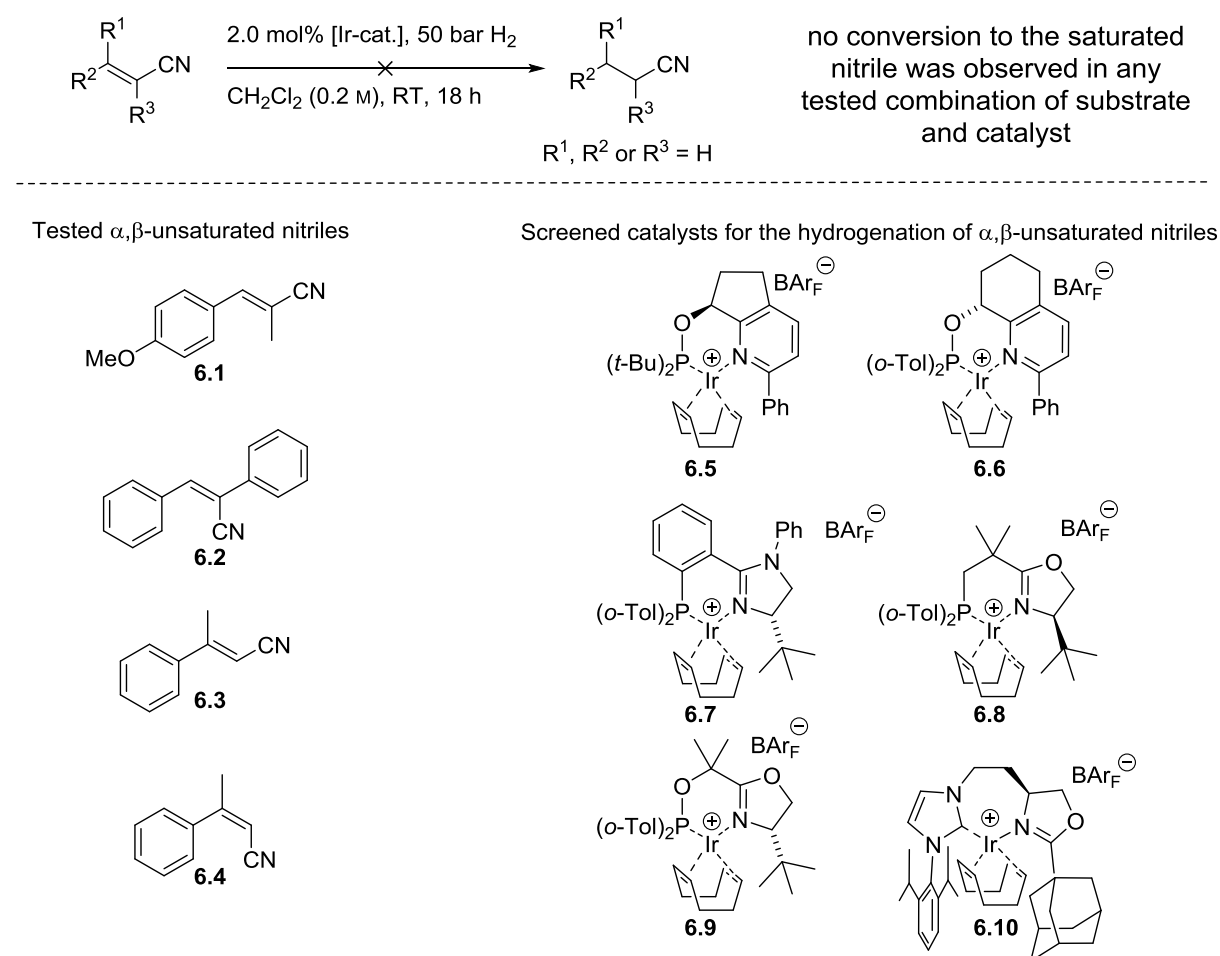
of the project discussed in this chapter was to study the application of iridium N,P ligand complexes in the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles.



**Scheme 6.2:** Different approaches to access enantiomerically enriched nitriles by conjugated reduction.

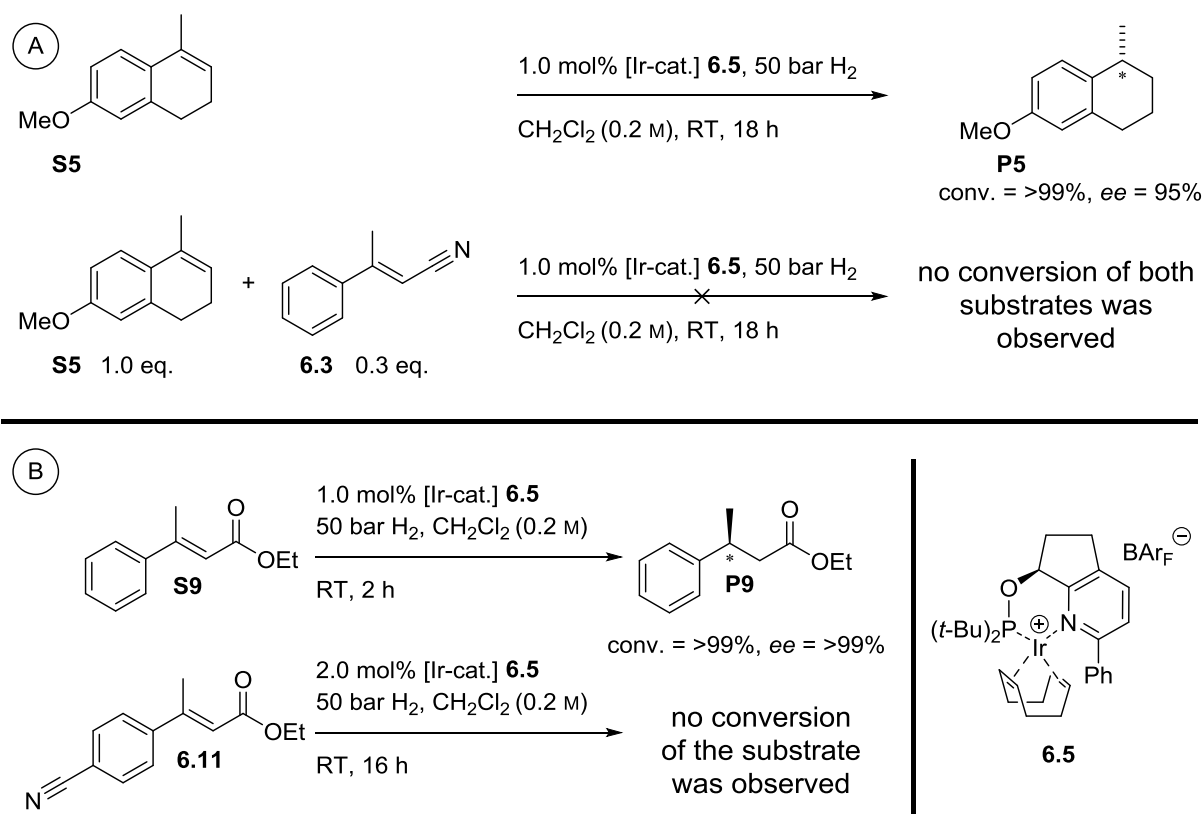
## 6.2 Hydrogenation of $\alpha,\beta$ -unsaturated nitriles with iridium complexes

At the beginning of this project several  $\alpha,\beta$ -unsaturated nitriles with different substitution patterns, electronic properties and double bond geometry were synthesized, to screen the performance of iridium-based catalysts in the hydrogenation of those substrates. All initial attempts to apply iridium-based complexes to the asymmetric hydrogenation of  $\alpha,\beta$ -unsaturated nitriles under standard reaction conditions, which had proved optimal for a wide variety of functionalized and unfunctionalized alkenes, were unsuccessful (2.0 mol% Ir-cat.,  $\text{CH}_2\text{Cl}_2$  (0.2 M), 50 bar  $\text{H}_2$  pressure, room temperature and 18 h). None of the many Ir-catalysts tested showed any reactivity towards this substrate class (scheme 6.3).



**Scheme 6.3:** Combinations of different substrates and catalysts screened.

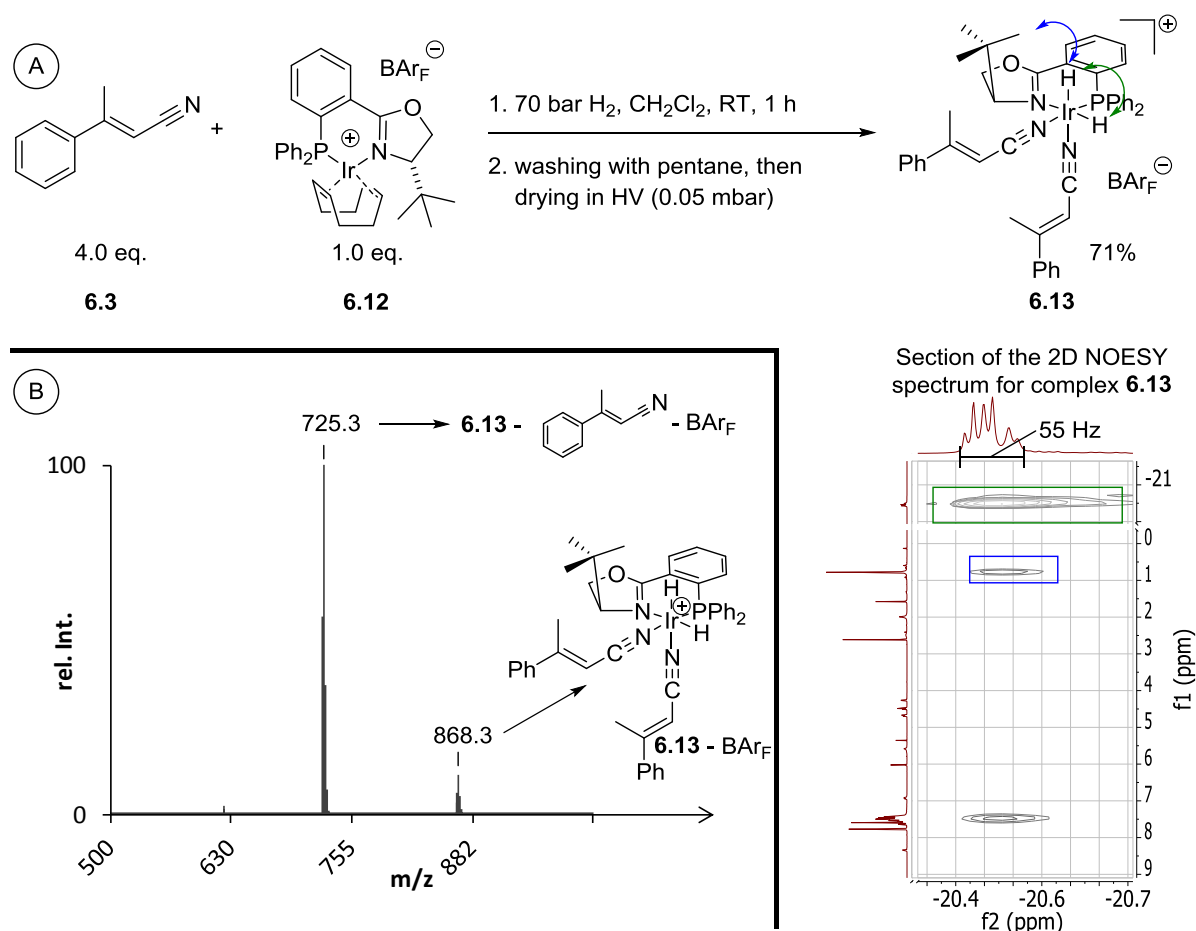
As previously mentioned, cyano groups have a high affinity to bind to transition metals and consequently the substrate might act as a catalyst inhibitor. Therefore, the hydrogenation of the cyclic olefin **S5**, which is reduced with full conversion using catalysts **6.5** under previously described reaction conditions (scheme 6.4, A), was investigated in the presence of (*E*)-3-phenylbut-2-enenitrile (**6.3**). Performing the reaction in the presence of 0.3 eq. of nitrile **6.3** relative to the cyclic olefin **S5**, neither conversion of the cyclic olefin to the tetrahydronaphthalene **P5**, nor any reduction of the unsaturated nitrile **6.3** was observed. This experiment confirmed the first assumption, that the  $\alpha,\beta$ -unsaturated nitrile **6.3** inhibits the catalytically active species produced from iridium complex **6.5** under hydrogen atmosphere. To further investigate if this catalyst deactivation is caused by interaction with the electron deficient double bond, the coordinating ability of the cyano group or due to combination of both effects further experiments were performed. For this purpose, an analog of the  $\alpha,\beta$ -unsaturated ester **6.11** bearing an additional cyano group at the *para*-position of the aryl moiety was synthesized. The  $\alpha,\beta$ -unsaturated ester **S9** was hydrogenated under previously mentioned standard conditions with full conversion using catalyst **6.5**.<sup>[52b]</sup> However, subjecting analog **6.11** bearing the cyano group even a higher catalyst loading and longer reaction times did not lead to any conversion of the substrate (scheme 6.4, B). Furthermore, the hydrogenation of ethyl (*E*)-3-phenylbut-2-enoate (**S9**) under the conditions depicted in scheme 6.4, B with additives, such as acetonitrile (0.1 eq.) or benzonitrile (0.1 eq.) was tested, but did not show any conversion. Similar reactivity was also observed by Crabtree and co-workers applying  $[\text{Ir}(\text{COD})(\text{PMePh})_2]\text{BF}_4$  in the hydrogenation of cyclohexene in the presence of 1 eq. acetonitrile with respect to metal.<sup>[22c]</sup>



**Scheme 6.4:** Hydrogenation of model substrate **S5** in the presence of the  $\alpha,\beta$ -unsaturated nitrile **6.3**, A; and the influence of an additional attached nitrile group to the model substrate **6.11**, B.

In order to explore the nature of the deactivated catalytic species, 70 bar hydrogen pressure was applied to a mixture of catalyst **6.12** and the  $\alpha,\beta$ -unsaturated nitrile **6.3** in a 1:4 ratio in  $\text{CH}_2\text{Cl}_2$ . After work-up (for details see the experimental part) a colorless product was obtained which was identified by 2D NMR analysis and ESI-MS spectrometry as the iridium(III)–dihydride-species **6.13** coordinated by two substrate molecules. This complex contains 18 valence electrons and is lacking a free coordination site that is necessary for catalytic activity. The COD ligand is reduced to cyclooctane and dissociates from the metal center. The resulting free coordination sites are occupied by two substrate molecules and two hydrides both in *trans*-orientation to the nitrogen atom. Based on the typical constant for a hydride in *trans*-position to a phosphorus atom (100–200 Hz)<sup>[112]</sup> and the width of the overlapping hydride signals (55 Hz), such an orientation of a hydride can be excluded. The configuration of the iridium center was assigned based on the NOESY contact of one hydride with the *tert*-butyl group on the dihydrooxazole unit (scheme 6.5, A). Additional data was gained by ESI-MS spectrometry. These data collected from the reaction mixture revealed two signals assigned to the iridium(III)–dihydride-species **6.13** minus the counterion and to the iridium(III)–dihydride-species **6.13** minus the counterion and one substrate molecule **6.3** (scheme 6.5, B). Furthermore, the orientation of the hydrides is in accordance with the major

species observed in the reaction of similar complexes with  $H_2$  investigated by Mazet *et al.* by NMR spectroscopy at  $-40\text{ }^\circ\text{C}$ . In this case iso-propyl PHOX is used as a ligand and THF adopts the position which is occupied by the cyano groups in complex **6.13**.<sup>[113]</sup>



**Scheme 6.5:** Isolated iridium(III)-dihydride-species **6.13** obtained by reaction of nitrile **6.3** with iridium complex **6.12** after applying 70 bar  $H_2$  pressure for 1 h and a section of the obtained NOESY spectrum, A; ESI-MS spectrum collected from the reaction mixture, B.

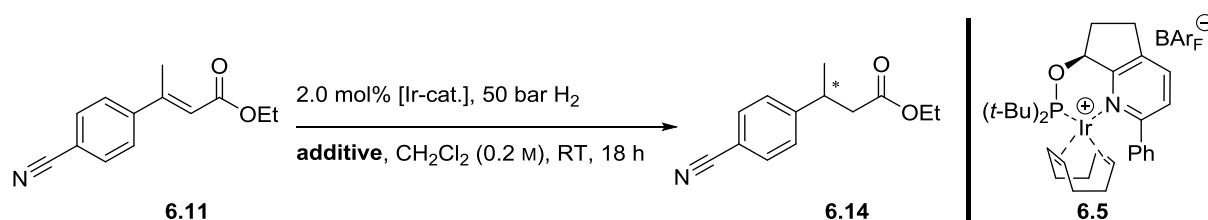
Based on these results, we concluded that it would be difficult to find an iridium complex enabling the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles under “standard” reaction conditions. An approach to overcome this problem could be the protection of the cyano group prior to hydrogenation, in order to prevent substrate coordination to the metal center and subsequent catalyst inhibition. In general, cyano groups have a high affinity to bind to many different transition metals and therefore this could be one approach to find a suitable “protection group”. However, such an approach would be unpractical as it would require large amounts of a second transition metal to be used as sacrificial binding species. In fact, considering a catalyst loading of 1 mol% of iridium complex, and the necessity of at least one free binding site, at least 99 mol% of a “protecting” metal would be needed to render the nitrile innocuous and allow the desired catalytic process. Recently, it was demonstrated by Stephan and co-workers, that tris(perfluorophenyl)borane can be used as protecting group for nitriles in the

hydrogenation of nitriles to amines by frustrated Lewis pairs.<sup>[114]</sup> Based on this publication the applicability of tris(perfluorophenyl)borane for iridium-catalyzed C–H activation reactions on substrates containing a cyano group was demonstrated by Dr. M. Parmentier.<sup>[115]</sup> Thus, the use of tris(perfluorophenyl)borane as additive in the hydrogenation of substrates bearing a cyano group was tested. In addition to tris(perfluorophenyl)borane, it was decided to test boron trifluoride, which is a slightly weaker Lewis acid but inexpensive and more convenient to handle.<sup>[116]</sup> Ethyl (*E*)-3-(4-cyanophenyl)but-2-enoate (**6.11**) was chosen as test substrate for two reasons:

1. This substrate should offer enough space between the cyano group and the double bond to avoid a strong shielding of the C=C bond by the potential protecting group.
2. The ester group should give some indication if this approach would be applicable in the presence of weakly nucleophilic oxygen atoms and therefore allow the application of the methodology to a sufficiently broad substrate range.

If this strategy showed encouraging results, extension to the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles would be the next logical step. Unfortunately, the hydrogenation of ethyl (*E*)-3-(4-cyanophenyl)but-2-enoate (**6.11**) in the presence of either tris(perfluorophenyl)borane or boron trifluoride as additives failed to afford the saturated ester **6.14** (table 6.1).

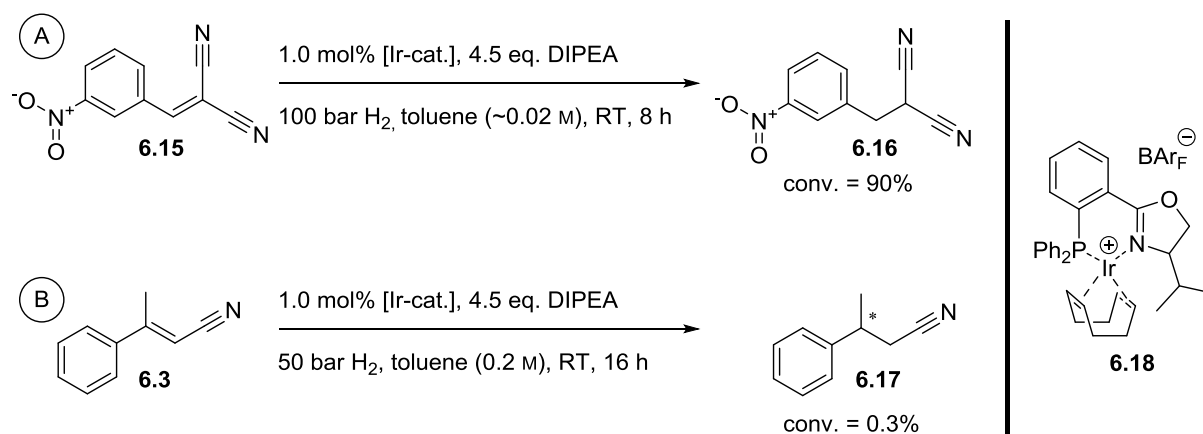
**Table 6.1:** Hydrogenation of substrate **6.11** in the presence of additives.



Entry	Additive	Conv. [%] <sup>[a]</sup>
1	none	0
2	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> (1.2 eq.)	0
3	BF <sub>3</sub> •Et <sub>2</sub> O (2.0 eq.)	0

[a] Determined by GC analysis on an achiral stationary phase.

Another approach to enable the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles was based on the work of Semeniuchenko *et al.*, who reported on the hydrogenation of electron deficient double bond by the use of the iridium PHOX catalyst **6.18** with *N,N*-diisopropylethylamine (DIPEA) as additive. The examples reported mainly dealt with different coumarin derivatives, but also  $\alpha,\beta$ -unsaturated dinitriles were tested (scheme 6.6, A).<sup>[117]</sup> Interestingly, the use of this additive was previously reported to deactivate iridium catalysts employed in the hydrogenation of unfunctionalized olefins.<sup>[118]</sup> Similar conditions to those used by Semeniuchenko *et al.* were tested in the hydrogenation of the model substrate **6.3**. In this case 0.3% conversion to the desired saturated nitrile **6.17** was observed. Although such a value accounts for less than one turnover of the catalyst, further investigations, were carried out (scheme 6.6, B).



**Scheme 6.6:** Hydrogenation conducted by Semeniuchenko *et al.*,<sup>[117a]</sup> A; hydrogenation conducted under similar reaction conditions, B.

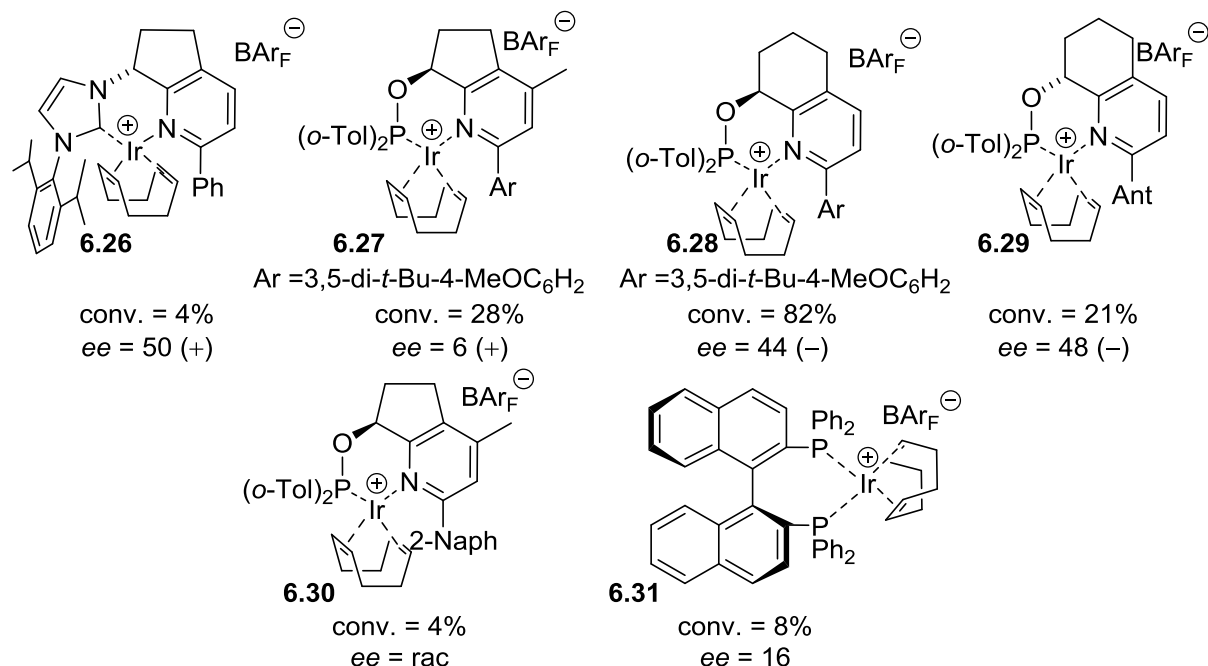
6.2.1 Hydrogenation of  $\beta,\beta$ -disubstituted  $\alpha,\beta$ -unsaturated nitriles

Several different N,P ligand complexes were screened in this reaction (table 6.2). Indeed several catalysts did show higher conversion compared to the Ir-PHOX complex **6.18**. Furthermore, the commercially available ThrePHOX-based catalyst **6.20** induced by far the highest selectivity while reaching almost full conversion. It should be mentioned, that this reaction emerged to be extraordinarily sensitive to small changes within the ligand structure. Only small variations showed immense differences in terms of enantioselectivity and conversion (table 6.2, **6.18** vs. **6.12** or **6.20** vs. **6.21**). Both steric and electronic factors seemed to play a role, but no clear trends could be deduced from the data.

**Table 6.2:** Catalyst screening for the hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3**.

 <b>6.18</b> conv. = 0.3% ee = n.d.	 <b>6.12</b> conv. = 10% ee = 34 (–)	 <b>6.5</b> conv. = 71% ee = 65 (–)	 <b>6.19</b> conv. = 18% ee = 13 (+)
 <b>6.20</b> conv. = 98% ee = 94 (+)	 <b>6.21</b> conv. = 8% ee = 47 (+)	 <b>6.6</b> conv. = 12% ee = rac	 <b>6.22</b> conv. = 2% ee = 2 (–)
 <b>6.23</b> conv. = >99% ee = 55 (–)	 <b>6.24</b> conv. = 5% ee = 8 (–)	 <b>6.25</b> conv. = 5% ee = 21 (–)	 <b>6.7</b> conv. = 24% ee = rac





Conversion determined by GC analysis on an achiral stationary phase. Enantiomeric excess determined by HPLC on a chiral stationary phase.

With these promising results in hand a detailed study was conducted using various derivatives of catalyst **6.20** that had been previously synthesized in the Pfaltz group (table 6.3). First, the removal of the methyl group on the dihydrooxazole unit revealed a drop from 94% to 88% *ee*. By using the diastereomeric ligand complex **6.33**, significantly lower conversion and considerable erosion of the *ee* compared to catalyst **6.20** was observed. Next, the influence of substituents on the aryl moiety directly attached to the dihydrooxazole unit was tested. Electron withdrawing groups led to significant lower selectivity and conversion whereas electron donating groups resulted in only slightly lower enantiomeric excesses (cat. **6.34-6.37**). All changes in the dibenzyl units of the ligand bridging the phosphonite with the dihydrooxazole part caused a significant drop in both conversion and enantioselectivity (cat. **6.38-6.42**). Therefore, iridium complex **6.20** still remained the most promising catalyst for this reaction.

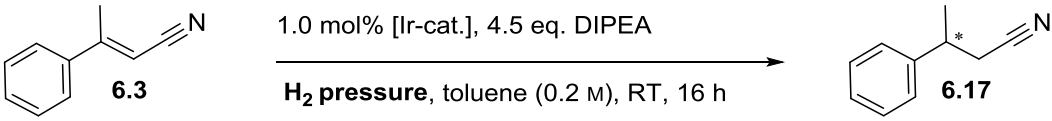
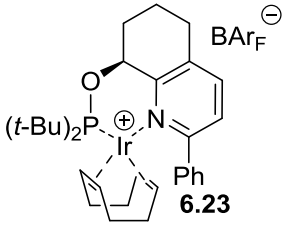
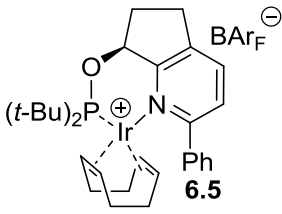
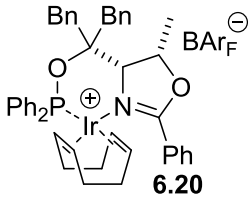
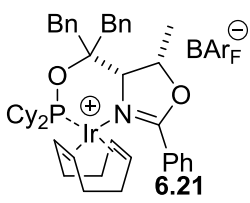
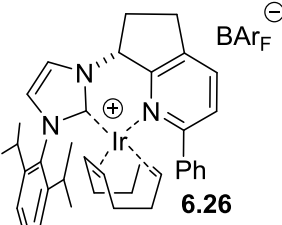
**Table 6.3:** Different derivatives of catalyst **6.20** screened in the hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3**.

<p><b>6.20</b> conv. = 98% ee = 94 (+)</p>	<p><b>6.32</b> conv. = 99% ee = 88 (+)</p>	<p><b>6.33</b> conv. = 19% ee = 33 (+)</p>	<p><b>6.34</b> conv. = 7% ee = 44 (+)</p>
<p><b>6.35</b> conv. = 17% ee = 16 (+)</p>	<p><b>6.36</b> conv. = 95% ee = 81 (-)</p>	<p><b>6.37</b> conv. = 88% ee = 93 (+)</p>	<p><b>6.38</b> conv. = 10% ee = 6 (-)</p>
<p><b>6.39</b> conv. = 64% ee = 62 (-)</p>	<p><b>6.40</b> conv. = 48% ee = 61 (-)</p>	<p><b>6.41</b> conv. = 6% ee = 26 (+) <i>t</i>-Bu</p>	<p><b>6.42</b> conv. = 24% ee = 23 (-)</p>

Conversion determined by GC analysis on an achiral stationary phase. Enantiomeric excess determined by HPLC on a chiral stationary phase.

Next, the reaction conditions were further investigated, using the most promising catalysts identified in the previous screening. An increase of hydrogen pressure from 50 to 100 bar resulted in higher conversion for all catalysts (table 6.4). Only a minimal effect of the hydrogen pressure on the enantioselectivity was observed but no general trend could be drawn. At 1 bar hydrogen pressure only catalyst **6.23** achieved still full conversion to the saturated nitrile **6.17**.

**Table 6.4:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3** at different hydrogen pressures.

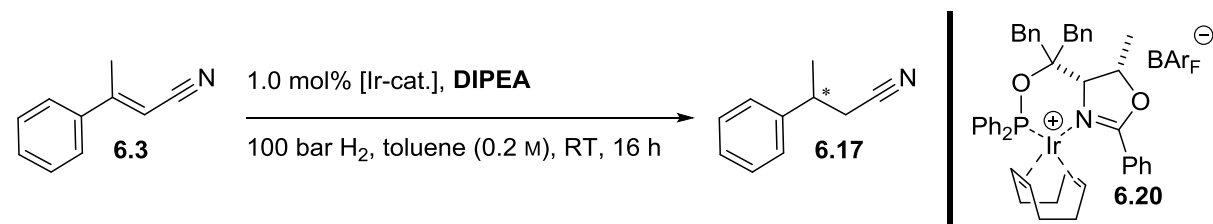
				
Entry	Catalyst	H <sub>2</sub> Pressure [bar]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	 <b>6.23</b>	1	>99	64 (–)
2		50	>99	55 (–)
3		100	>99	58 (–)
4	 <b>6.5</b>	50	71	65 (–)
5		100	64	69 (–)
6	 <b>6.20</b>	1	34	97 (+)
7		50	98	94 (+)
8		100	>99	94 (+)
9	 <b>6.21</b>	50	4	50 (+)
10		100	18	52 (+)
11	 <b>6.26</b>	50	4	50 (+)
12		100	18	52 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

As next parameter, the amount of DIPEA used in the reaction was varied (table 6.5), which turned out to have a crucial influence on the outcome of the hydrogenation. Both increasing and decreasing the equivalents of DIPEA resulted in significantly reduced conversion combined with a drop in enantioselectivity (entries 2-3 and 5-7). Even employing DIPEA as the reaction medium (entry 1) allowed for the reaction to occur but conversion remained below 50% and the enantioselectivity dropped to 83% *ee*. In the case of 0.5 eq. and 0.1 eq.

DIPEA only 95% and 70% conversion was observed, but this showed that the base can be applied in substoichiometric amounts (entries 6 and 7).

**Table 6.5:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3** using different stoichiometry of DIPEA.

			
Entry	DIPEA [eq.]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	Solvent	41	83 (+)
2	18	74	88 (+)
3	9.0	85	88 (+)
4	4.5	>99	95 (+)
5	1.5	99	82 (+)
6	0.5	95	75 (+)
7	0.1	70	69 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

Thereafter, the influence of different nitrogen containing bases (table 6.6) was tested. Triethylamine performed almost as well as DIPEA in combination with all catalysts. The use of *N*-isopropyl-*N*-methyl-*tert*-butylamine, which can form different diastereoisomers upon coordination to the metal center, resulted in a drop of the enantiomeric excess with all tested catalysts. 1,8-Diazabicycloundec-7-ene (DBU) as additive showed almost no conversion. Interesting results were obtained applying 2,6-lutidine. The two ThrePHOX-based catalysts showed no activity, whereas a significantly increased selectivity was found for the two pyridine-based catalysts with up to 93% *ee* for catalyst **6.5** but only 27% conversion. Based on these results, different structures related to lutidine, like pyridine or 2,6-di-*tert*-butylpyridine, were tested. The use of pyridine as additive resulted in almost complete loss of reactivity whereas 2,6-di-*tert*-butylpyridine gave full conversion in combination with catalyst **6.23** and 82% *ee*.

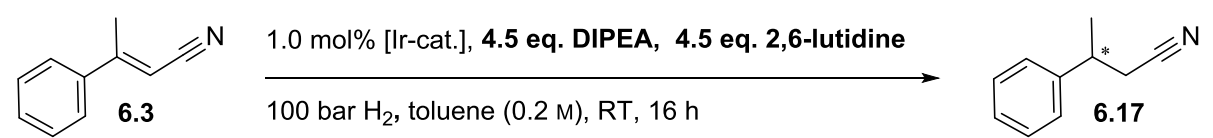
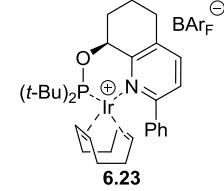
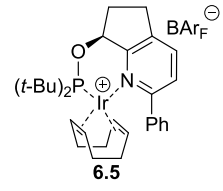
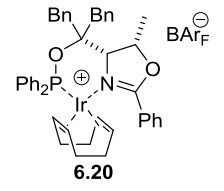
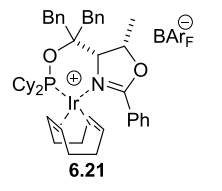
**Table 6.6:** Different bases applied to the hydrogenation of (*E*)-3-phenylbut-2-enenitrile (**6.3**).

Base	 6.23		 6.5		 6.20		 6.21	
	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>
DIPEA	>99	58 (–)	64	69 (–)	>99	94 (+)	8 <sup>[c]</sup>	47 (+) <sup>[c]</sup>
Et <sub>3</sub> N	>99	59 (–)	>99	71 (–)	>99	95 (+)	13	43 (+)
<i>t</i> -Bui-PrMeN	>99	53 (–)	58	29 (–)	>99	88 (+)	24	2 (–)
DBU	4	n.d.	4	n.d.	4	n.d.	6	n.d.
1,2,2,6,6-Pentamethylpiperidine	>99	57 (–)	38	65 (–)	>99	94 (+)	24	13 (+)
2,6-Lutidine	>99	67 (–)	27	93 (–)	1	n.d.	0	--
Pyridine	2	n.d.	0	--	--	--	--	--
2,6-Di- <i>tert</i> -butylpyridine	>99	82 (–)	5	91 (–)	--	--	--	--

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase; [c] Reaction performed at 50 bar H<sub>2</sub> pressure.

Based on the results obtained from the additive screening with 2,6-lutidine, we tried to increase the reactivity and selectivity using a mixture of DIPEA and 2,6-lutidine. Indeed, three out of the four tested catalysts showed higher enantioselectivity with this approach (table 6.7). Only for catalyst **6.20**, which showed so far the highest enantioselectivity, a drop of both *ee* and activity was observed.

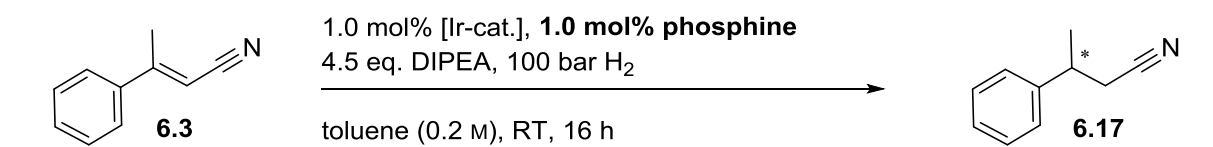
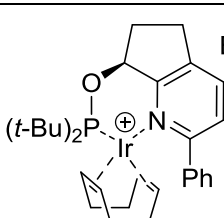
**Table 6.7:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3** applying a mixture of DIPEA and 2,6-lutidine.

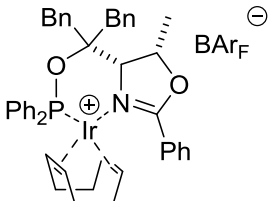
									
Base									
	6.23	6.5	6.20	6.21					
	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	
4.5 eq. DIPEA and 4.5 eq. 2,6-lutidine	>99	66 (–)	63	82 (–)	46	92 (+)	5	72 (+)	
4.5 eq. DIPEA	>99	59 (–)	60	71 (–)	>99	94 (+)	18	43 (+)	

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

Based on the results obtained by the addition of 2,6-lutidine, the significantly increased selectivity might be explained by a coordination of lutidine to the metal center. In order to test the influence of other coordinating ligands, experiments with 1.0 mol% of different phosphines were performed (table 6.8). The combination of tricyclohexylphosphine with catalyst **6.5** showed higher conversion (>99%) compared to the reaction without the phosphine (64%) but lower enantioselectivity (table 6.8, entry 2 vs. table 6.4, entry 5). For the threonine-based catalyst **6.20** both triphenylphosphine and tricyclohexylphosphine resulted in significantly lower conversion.

**Table 6.8:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3** using phosphines as additives.

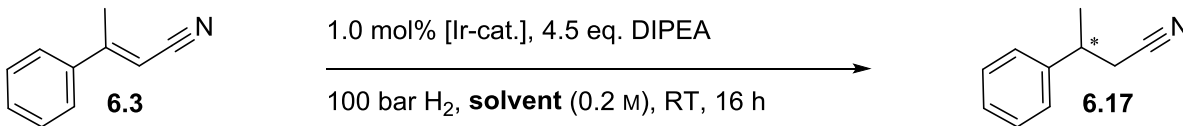
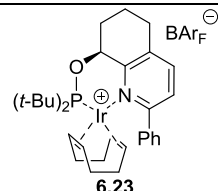
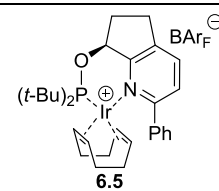
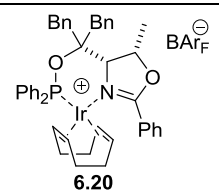
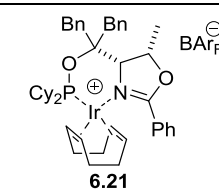
				
Entry	Catalyst	Phosphine	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>
1		PPh <sub>3</sub>	24	15 (–)
2		PCy <sub>3</sub>	>99	62 (–)

3		PPh <sub>3</sub>	1	n.d.
4		PCy <sub>3</sub>	19	93 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

As solvents can have a significant impact on the coordinating ability of ligands, the solvent effect in the hydrogenation of (*E*)-3-phenylbut-2-enenitrile (**6.3**) with different ligand complexes was investigated (table 6.9). The range of solvents tolerated proved to be remarkably broad. Surprisingly, even in strongly coordinating solvents such as methanol or acetonitrile, which are known to inhibit iridium-based catalysts, catalytic activity was retained. Among all polar protic and aprotic solvents that were tested, only DMSO was found to be unsuitable. The highest *ee* was observed in DMF with catalyst **6.20** (97%), but the reaction did not go to completion. Full conversion and excellent enantioselectivities of 94-95% *ee* were achieved in alcoholic solvents and in even water. Although, the substrate is not soluble in water, the remarkable water tolerance of this catalyst system is an attractive feature enhancing its scope and practicality. Only trifluoroethanol resulted in a significant drop of enantioselectivity for the threonine-based catalyst **6.20**. In this solvent catalyst **6.5**, which was less selective in all other solvents, showed the highest enantiomeric excess (79%).

**Table 6.9:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3** in different solvents.

									
Solvent									
	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	
Toluene	>99	58 (–)	64	69 (–)	>99	94 (+)	8 <sup>[c]</sup>	47 (+) <sup>[c]</sup>	
CH <sub>2</sub> Cl <sub>2</sub>	>99	60 (–)	75	32 (–)	>99	93 (+)	17	62 (+)	
THF	94	59 (–)	18	51 (–)	>99	96 (+)	18	16 (+)	

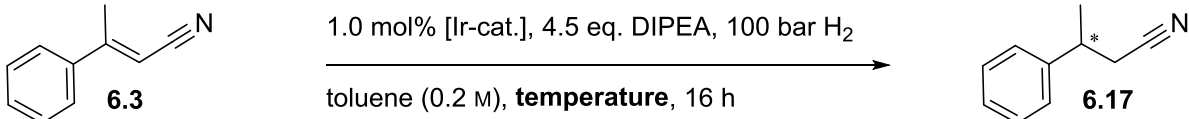
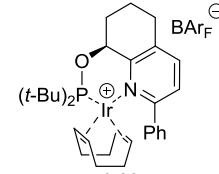
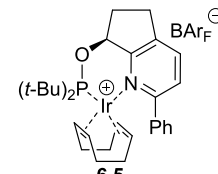
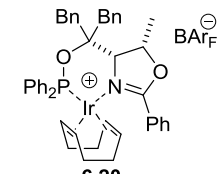
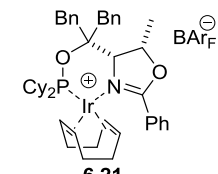
CF <sub>3</sub> CH <sub>2</sub> OH	>99	70 (–)	81	79 (–)	99	68 (+)	10	4 (+)
MeOH	>99	66 (–)	84	62 (–)	>99	95 (+)	28	n.d.
<i>i</i> -PrOH	>99	66 (–)	16	71 (–)	>99	94 (+)	47	63 (+)
Ethanol	>99	69 (–)	97	62 (–)	>99	95 (+)	29	60 (+)
H <sub>2</sub> O	--	--	--	--	>99	95 (+)	--	--
DMF	60	71 (–)	2	n.d.	85	97 (–)	3	n.d.
DMSO	0	--	0	--	0	--	0	--
CH <sub>3</sub> CN	>99	49 (–)	84	10 (–)	>99	87 (+)	25	62 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase; [c] Reaction performed at 50 bar H<sub>2</sub> pressure.

Lowering the temperature is known to often have a positive impact on the enantioselectivity. Indeed, the *ee* could be further increased by carrying out the reaction at lower temperature (table 6.10). Hydrogenations at –8 °C revealed for all tested catalysts a higher enantiomeric excess. For catalyst **6.20** even 99% *ee* was observed but conversion remained below 50%. Therefore, the combination of the most suitable parameters obtained from the previous screening with catalyst **6.20** in methanol at 0 °C was explored. Indeed, under these reaction conditions full conversion with 98% enantiomeric excess was reached (table 6.10).



**Table 6.10:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3** at reduced temperature.

								
Temp.	 6.23	 6.5	 6.20	 6.21				
	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>
RT	>99	58 (–)	64	69 (–)	>99	94 (+)	8 <sup>[c]</sup>	47 (+) <sup>[c]</sup>
0 °C	--	--	--	--	>99 <sup>[d]</sup>	98 (+) <sup>[d]</sup>	--	--
–8 °C	91	75 (–)	21	94 (–)	48	99 (+)	2	82 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase; [c] Reaction run at 50 bar H<sub>2</sub> pressure; [d] Reaction performed in MeOH.

Combining the optimal reaction parameters identified from the previous screenings of substrate **6.3**, the scope of catalyst **6.20** in the hydrogenation of different  $\alpha,\beta$ -unsaturated nitriles was tested. These substrates were almost exclusively synthesized by Horner–Wadsworth–Emmons reaction from the corresponding arylketone precursors. First, the different substitution patterns on the aryl ring and the influence of electron withdrawing and electron donating groups were investigated (table 6.11). Changing the double bond geometry from *trans* to *cis* caused a large drop in enantioselectivity and conversion (**6.43**). Introduction of an *ortho* substituent into the phenyl group, which destabilizes a coplanar arrangement of the C=C bond and the aromatic  $\pi$ -system and causes higher steric hindrance around the target C=C bond, also reduced the reactivity and *ee*, but to a lower extent (**6.44** and **6.45**). Electron donating or withdrawing substituents in *meta*- or *ortho*-position of the aryl moiety had no or only a minor influence on the conversion and the enantioselectivity (**6.46–6.51**). These substrates were reduced with *ees* between 95% and 98% with full conversion.

**Table 6.11:** Substrate scope of the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles.

<div>□:T: 25 °C</div> <div>conv. = &gt;99%</div> <div>ee = 95% (+)</div>	<div>□:T: 0 °C</div> <div>conv. = &gt;99%</div> <div>ee = 98% (+)</div>	<div>□:T: 25 °C</div> <div>conv. = 67%</div> <div>ee = 25% (-)</div>	
<div>□:T: 25 °C</div> <div>conv. = 96%</div> <div>ee = 78%</div>	<div>□:T: 0 °C</div> <div>conv. = 71%</div> <div>ee = 82%</div>	<div>■:T: 25 °C</div> <div>conv. = 54%</div> <div>ee = 52%</div>	
<div>■:T: 25 °C</div> <div>conv. = &gt;99%</div> <div>ee = 95% (S)</div>	<div>■:T: 0 °C</div> <div>conv. = &gt;99%</div> <div>ee = 97% (S)</div>	<div>■:T: 25 °C</div> <div>conv. = &gt;99%</div> <div>ee = 96% (+)</div>	<div>■:T: 0 °C</div> <div>conv. = &gt;99%</div> <div>ee = 96% (+)</div>
<div>■:T: 25 °C</div> <div>conv. = &gt;99%</div> <div>ee = 92% (+)</div>	<div>■:T: 0 °C</div> <div>conv. = 97%</div> <div>ee = 96% (+)</div>	<div>■:T: 25 °C</div> <div>conv. = &gt;99%</div> <div>ee = 97% (-)</div>	<div>■:T: 0 °C</div> <div>conv. = &gt;99%</div> <div>ee = 98% (-)</div>
<div>□:T: 25 °C</div> <div>conv. = &gt;99%</div> <div>ee = 94% (-)</div>	<div>□:T: 0 °C</div> <div>conv. = &gt;99%</div> <div>ee = 97% (-)</div>	<div>■:T: 25 °C</div> <div>conv. = &gt;99%</div> <div>ee = 97% (+)</div>	<div>■:T: 0 °C</div> <div>conv. = &gt;99%</div> <div>ee = 98% (+)</div>

All conversions determined by GC on an achiral stationary phase. Enantiomeric excess determined by HPLC on a chiral stationary phase.

Next, the influence of the alkyl substituent on the C=C bond was investigated (table 6.12). Replacing the methyl group by iso-propyl, similar results as for *ortho*-substitution on the aryl moiety was observed. Since it is known that an iso-propyl group in this position results in a similar change in geometry to that caused by an *ortho*-substitution on the aryl moiety,<sup>[119]</sup> a drop of enantioselectivity was expected for these substrates. Other alkyl substituents, smaller than iso-propyl but larger than methyl, such as ethyl, *n*-propyl or *sec*-butyl on the C=C bond revealed full conversion with similar or even higher enantiomeric excess between 96% and 99% (**6.54**, **6.55** and **6.56**).

**Table 6.12:** Substrate scope of the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles with different alkyl substituents at the  $\beta$ -position.

■:T: 25 °C conv. = >99% ee = 63% (-)	■:T: 0 °C conv. = 74% ee = 72% (-)	□:T: 25 °C conv. = 16% ee = n.d.	□:T: 0 °C conv. = 3 ee = 25 (-)
■:T: 25 °C conv. = >99% ee = 98% (-)	□:T: 0 °C conv. = >99% ee = 99% (+)	□:T: 25 °C conv. = >99% ee = 96% (+)	■:T: 0 °C conv. = >99% ee = 98% (-)
■:T: 25 °C conv. = >99% ee = 96% (+)		■:T: 0 °C conv. = 97% ee = 98% (+)	

All conversions determined by GC on an achiral stationary phase. Enantiomeric excess determined by HPLC on a chiral stationary phase.

Next, the functional group tolerance of this reaction was tested (table 6.13). Substrates containing a pyridine, primary amine or diene unit, which have been recognized as challenging substrates under base-free conditions,<sup>[24, 77, 118]</sup> also showed significantly reduced catalyst reactivity was observed under base-promoted conditions (**6.65**, **6.66** and **6.67**). Despite these results, this catalyst system showed high functional group tolerance overall, as exemplified by the fluoro-, chloro-, bromo-, acetamido-, carbomethoxy-, cyano-, and nitro-substituted compounds that were successfully hydrogenated (**6.57–6.63**). In contrast to the substrate **6.63** containing a nitro-group in the *meta*-position, the *para*-substituted analog **6.64** showed almost no conversion.

**Table 6.13:** Substrate scope of the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles containing different functional groups.

Groups.

1.0 mol% [Ir-cat.], 4.5 eq. DIPEA  
100 bar H<sub>2</sub>, MeOH (0.2 M), T, 4 h

6.20

□ (S,S) ■ (R,R)

6.57

□: T: 25 °C    □: T: 0 °C  
 conv. = >99%    conv. = 99%  
 ee = 90% (+)    ee = 96% (+)

6.58

■: T: 25 °C    ■: T: 0 °C  
 conv. = >99%    conv. = >99%  
 ee = 97% (+)    ee = 97% (+)

6.59

■: T: 25 °C    ■: T: 0 °C  
 conv. = >99%    conv. = >99%  
 ee = 96% (+)    ee = 98% (+)

6.60

■: T: 25 °C    ■: T: 0 °C  
 conv. = >99%    conv. = 98%  
 ee = 97% (-)    ee = 98% (-)

6.61

■: T: 25 °C    ■: T: 0 °C  
 conv. = >99%    conv. = 41%  
 ee = 94% (+)    ee = 95% (+)

6.62

■: T: 25 °C    ■: T: 0 °C  
 conv. = >99%    conv. = >99%  
 ee = 98% (+)    ee = 98% (+)

6.63

■: T: 25 °C    ■: T: 0 °C  
 conv. = >99%    conv. = >99%  
 ee = 93% (-)    ee = 93% (-)

6.64

■: T: 25 °C  
 conv. = 6%  
 ee = n.d.

6.65

□: T: 25 °C  
 conv. = 0%  
 ee = --

6.66

□: T: 25 °C  
 conv. = 33%  
 ee = n.d.

6.67

□: T: 25 °C  
 conv. = 7%, ee = n.d.  
 hydrogenation of both  
 double bonds was observed

All conversions determined by GC on an achiral stationary phase. Enantiomeric excess determined by HPLC or GC on a chiral stationary phase.

In a next step, the amount of DIPEA and the catalyst loading were investigated (table 6.14). In methanol with 1.0 mol% catalyst the amount of DIPEA could be reduced to 0.1 eq. without affecting the *ee* and conversion (entries 1-5). This is a significant advantage compared to the reactions in toluene, in which the outcome of the reaction is significantly dependent on the stoichiometry of DIPEA. In methanol even in the absence of DIPEA the reaction went to completion, but the *ee* dropped from 95% to 86% (entry 6). Furthermore, the catalyst loading could be considerably reduced. By using only 0.23 eq. of DIPEA, as little as 0.05 mol% catalyst was enough to achieve full conversion with an enantiomeric excess of 95% within 16 h (entry 15). Further experiments in this direction showed that by increasing the reaction time even with 0.005 mol% catalyst loading 96.5% conversion and 95% *ee* was observed (entry 17). This corresponds to 19300 turnovers of the catalyst.

**Table 6.14:** Variation of catalyst loading and the DIPEA amount in methanol for the hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3**.

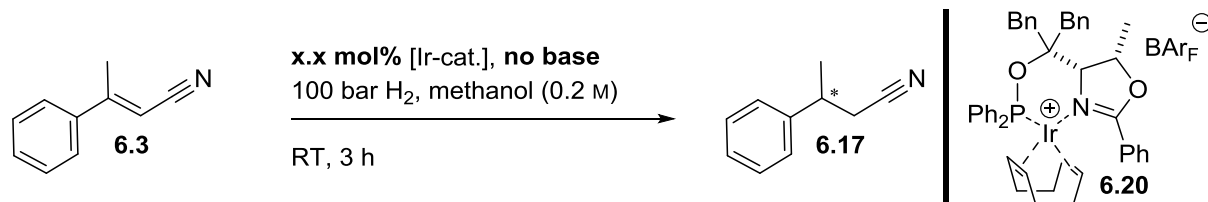
Entry	Catalyst	Time [h]	Cat. loading [mol%]	DIPEA [eq.]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1		16	1.0	18	>99	96 (+)
2		16	1.0	4.5	>99	95 (+)
3		16	1.0	1.5	>99	95 (+)
4		16	1.0	0.5	>99	95 (+)
5		16	1.0	0.1	>99	95 (+)
6		16	1.0	none	>99	86 (+)
7		4	0.5	0.5	>99	96 (–)
8		4	0.2	0.5	>99	96 (–)
9		4	0.1	0.5	>99	95 (–)
10		4	0.05	0.5	97	96 (–)
11		4	0.1	1	>99	97 (–)
12		4	0.1	0.5	>99	97 (–)
13		4	0.1	0.1	>99	96 (–)
14		4	0.1	0.01	>99	96 (–)
15		16	0.05	0.23	>99	96 (–)
16		72	0.05	0.005	99.5	96 (–)
17 <sup>[c]</sup>		112	0.005	0.023	96.5	95 (–)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase; [c] Reaction run on 1.5 mmol scale.

The observation that the reaction in methanol could be carried out in the absence of DIPEA, prompted a more detailed investigation of the possibility to avoid the use of a base. Therefore, the catalyst loading in the absence of DIPEA was systematically reduced while keeping the reaction time constant (table 6.15). While the conversion gradually decreased lowering the

catalyst loading, the enantiomeric excess followed the opposite trend, reaching 95% at 49% conversion with 0.05 mol% catalyst loading.

**Table 6.15:** Hydrogenations of  $\alpha,\beta$ -unsaturated nitrile **6.3** at reduced catalyst loadings in the absence of an additional base.

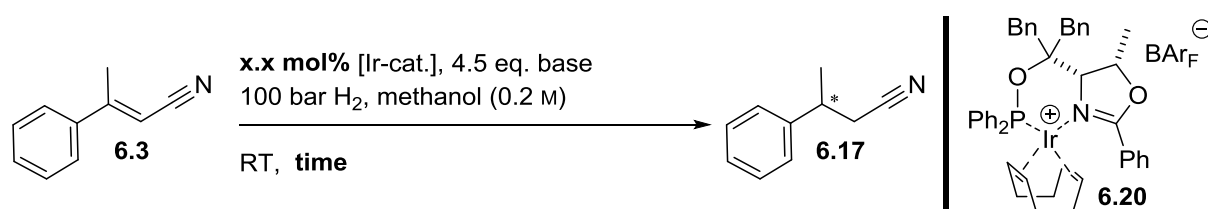


Entry	Cat. loading [mol%]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	1.0	>99	86 (+)
2	0.5	92	86 (+)
3	0.1	76	93 (+)
4	0.05	49	95 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

The use of methanol as solvent allowed for the employment of different bases which are not soluble in toluene. In this context, different inorganic bases were screened (table 6.16). In general, similar results to those observed in pure methanol were obtained. Only in the presence of  $NaHCO_3$  a higher selectivity of 92% *ee* was achieved.

**Table 6.16:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3** using different inorganic bases.



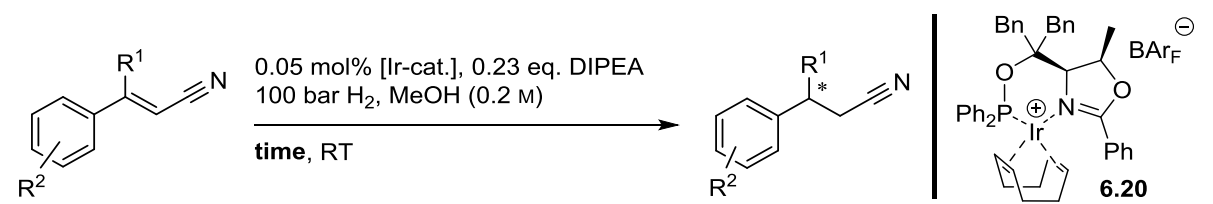
Entry	Base	Cat. loading [mol%]	Time [h]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	$Na_2CO_3$	1.0	16	>99	89 (+)
2	$Na_2CO_3$	0.2	3	>99	86 (+)
3	$Na_2CO_3$	0.1	3	>99	87 (+)

4	$\text{Na}_2\text{CO}_3$	0.05	3	88	88 (+)
5	$\text{NaOH}$	1.0	16	>99	85 (+)
6	$\text{NaOMe}$	1.0	16	>99	66 (+)
7	$\text{NaHCO}_3$	1.0	16	>99	92 (+)
8	$\text{NaHCO}_3$	0.1	3	98	90 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

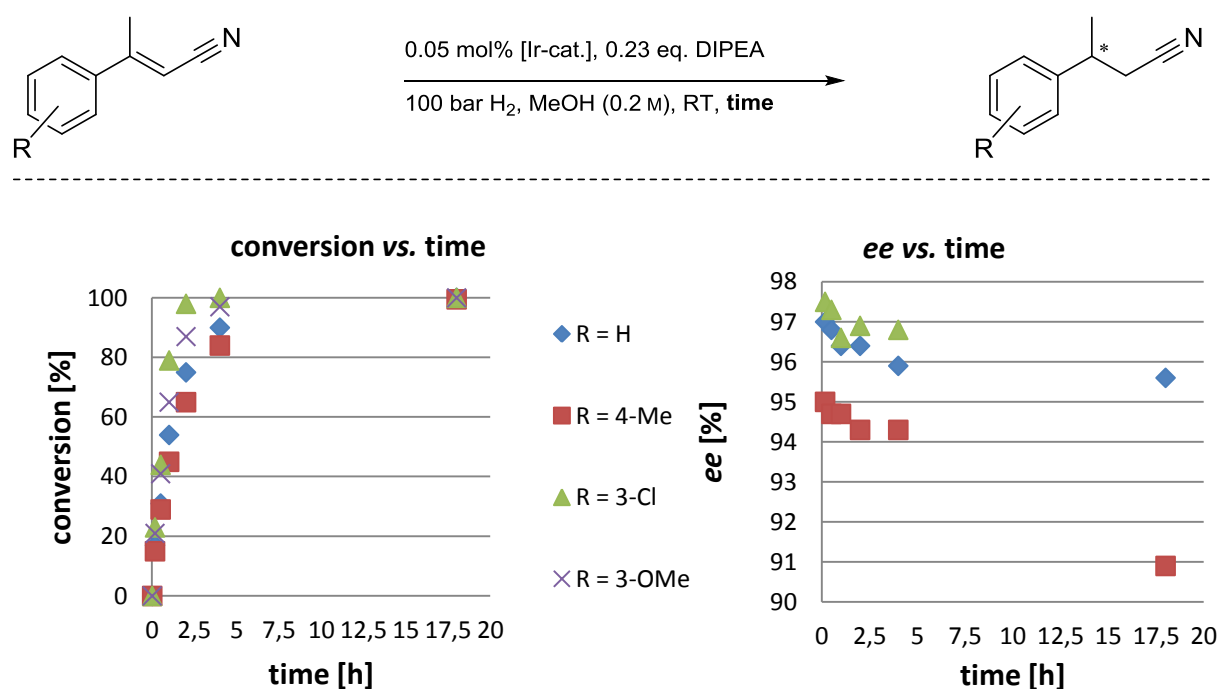
In a next study, the low catalyst loading of 0.05 mol% was applied to different substrates in the presence of 0.23 mol% of DIPEA (table 6.17). Remarkably, for all substrates 99% to full conversion was achieved with similar enantioselectivity. Only for substrate **6.46** containing a methyl substituent in the *para*-position of the aryl moiety a drop in enantioselectivity from 95% to 91% was observed compared to the reaction at 1.0 mol% catalyst loading and 4.5 eq. DIPEA (table 6.12, entry 3 vs. table 6.12, **6.46**).

**Table 6.17:** Hydrogenation of various of  $\alpha,\beta$ -unsaturated nitriles at 0.05 mol% catalyst loading.

					
Entry	R <sup>1</sup>	R <sup>2</sup>	Time [h]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	Me	H	4	97	96 (–)
2	Me	H	16	>99	96 (–)
3	Me	4-Me	18	>99	91 (S)
4	Me	4-Br	16	>99	96 (+)
5	Me	4-NHCOCH <sub>3</sub>	16	>99	97 (–)
6	Me	3-OMe	18	>99	95 (+)
7	Me	3-Cl	18	>99	96 (+)
8	Et	H	18	99	97 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

Subsequently, the kinetics of the reaction was investigated varying the electron density on the aryl substituent (graph 6.1). In general no clear trend was observed but it became obvious that 18 h were not mandatory to achieve complete conversion for all substrates. For example the more electron deficient double bond of substrate **6.51** containing a chlorine atom at the *meta*-position of the aryl ring showed 98% conversion after only 2 hours at 0.05 mol% catalyst loading. In addition, a general erosion of the enantiomeric excess over time was observed, in line with the observation that the lowest enantiomeric excess was registered for the substrate with the slowest reaction rate. To found out whether the drop in enantioselectivity was a result of racemization, a control experiment was performed: the enantioenriched nitrile **6.17** was stirred for 16 h under hydrogenation conditions. As no erosion of the enantiomeric excess after that time was observed, a postreaction racemization could be excluded.



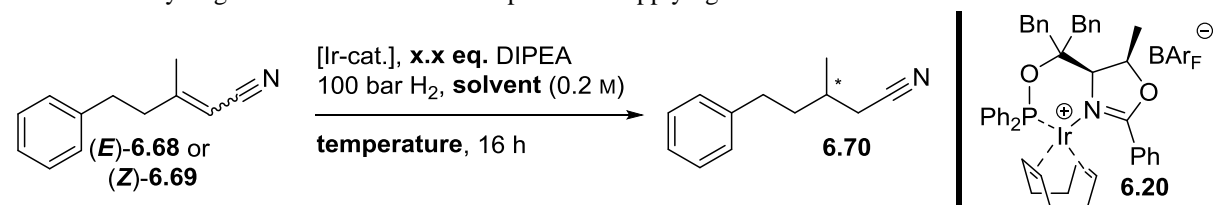
**Graph 6.1:** Kinetic data obtained for the hydrogenation of different substrates. Due to overlap with the substrate for *meta*-methoxy substitution the *ee* was not determined for samples revealing incomplete conversion.

Further investigations focused on the hydrogenation of  $\beta,\beta$ -dialkyl-substituted acrylonitriles (table 6.18). In contrast to substrates containing an aryl substituent on the C=C bond they exhibited lower reactivity and required 2.0 mol% of catalyst and longer reaction time to reach full conversion at 0 °C. The enantioselectivities were also lower compared to those obtained in the hydrogenation of the phenyl methyl analog **6.3**. Interestingly, the (*Z*)-isomer (*Z*)-**6.69** afforded higher *ee* than the (*E*)-isomer (*E*)-**6.68**, contrary to the results obtained with (*E*)-**6.3** and (*Z*)-**6.43**. The best results were achieved at 0 °C, which led to the saturated nitrile **6.70**



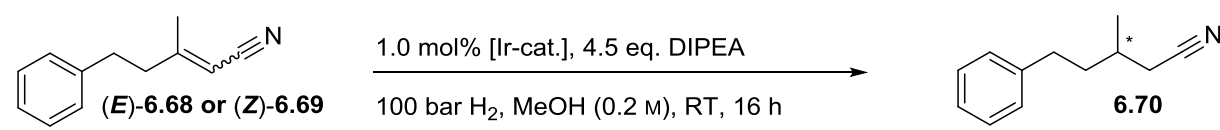
with 82% *ee* and full conversion. At  $-15\text{ }^{\circ}\text{C}$  the *ee* raised to 88%, but conversion amounted to only 51%. The hydrogenation product obtained in this case is known as Citralis nitrile<sup>®</sup>, a compound that frequently finds application in fragrances.<sup>[120]</sup>

**Table 6.18:** Hydrogenation of Citralis nitrile<sup>®</sup> precursors applying different reaction conditions.

							
Entry	T [ $^{\circ}\text{C}$ ]	Double bond geometry	Cat. loading [mol%]	Solvent	DIPEA [eq.]	Conv. [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[a]</sup>
1	25	( <i>E</i> )	1.0	MeOH	4.5	99	48 (+)
2	0	( <i>E</i> )	2.0	MeOH	4.5	>99	64 (+)
3	0	( <i>E</i> )	2.0	MeOH	0.5	92	65 (+)
4	0	( <i>E</i> )	1.0	MeOH	0.1	31	70 (+)
5	$-15$	( <i>E</i> )	2.0	MeOH	9.0	32	79 (+)
6	0	( <i>E</i> )	2.0	<i>i</i> -PrOH	9.0	>99	68 (+)
7	25	( <i>Z</i> )	1.0	MeOH	4.5	>99	64 (–)
8	0	( <i>Z</i> )	2.0	MeOH	4.5	>99	82 (–)
9	0	( <i>Z</i> )	2.0	MeOH	0.5	98	78 (–)
10	0	( <i>Z</i> )	1.0	MeOH	0.1	33	79 (–)
11	$-15$	( <i>Z</i> )	2.0	MeOH	9.0	51	88 (–)
12	0	( <i>Z</i> )	2.0	<i>i</i> -PrOH	9.0	>99%	75 (–)

[a] Determined by GC analysis on a chiral stationary phase.

Furthermore, different catalysts were screened in the hydrogenation of the Citralis nitrile<sup>®</sup> precursors (*E*)-**6.68** and (*Z*)-**6.69** (table 6.19). The catalysts showed the same order of selectivity as observed for the phenyl methyl analog **6.3** and no higher enantiomeric excess was reached. Therefore, no further screening of other catalysts was conducted.

**Table 6.19:** Hydrogenation of Citralis nitrile® precursors (*E*)-**6.68** and (*Z*)-**6.69** with different catalysts.

Entry	Catalyst	Double bond geometry	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[a]</sup>
1		( <i>E</i> )	>99	30 (+)
2		( <i>Z</i> )	>99	2 (+)
3		( <i>E</i> )	33	19 (+)
4		( <i>Z</i> )	65	14 (–)
5		( <i>E</i> )	99	48 (+)
6		( <i>Z</i> )	>99	65 (–)
7		( <i>E</i> )	11	26 (–)
8		( <i>Z</i> )	21	34 (+)

[a] Determined by GC analysis on a chiral stationary phase.

6.2.2 Hydrogenation of  $\alpha,\beta$ -disubstituted  $\alpha,\beta$ -unsaturated nitriles

Having investigated so far  $\beta,\beta$ -disubstituted substrates, the focus was set on substrates containing a substituent at the  $\alpha$ -position of the C=C bond. First, different catalysts in the hydrogenation of (*Z*)-2,3-diphenylacrylonitrile (**6.2**) were tested. Out of eight tested catalysts, enantioselectivities below 20% were obtained (table 6.20). Furthermore, the reactivity of each catalyst observed for substrate **6.2** was completely different compared to the phenyl methyl analog **6.3**. For this substrate, only the pyridine-based catalysts achieved full conversion, whereas the ThrePHOX-based catalysts **6.21** and **6.20** gave only 25% product.

**Table 6.20:** Catalyst screening in the hydrogenation of (*Z*)-2,3-diphenylacrylonitrile (**6.2**).

<p>conv. = &gt;99% ee = <i>rac</i></p>		<p>conv. = &gt;99% ee = 6%</p>	
<p>Ar = 4-MeOC<sub>6</sub>H<sub>4</sub> <b>6.72</b> conv. = &gt;99% ee = 11%</p>		<p><b>6.26</b> conv. = &gt;99% ee = 14</p>	
<p><b>6.21</b> conv. = 25% ee = <i>rac</i></p>		<p><b>6.20</b> conv. = 25% ee = 18%</p>	

Conversion determined by GC analysis on an achiral stationary phase. Enantiomeric excess determined by HPLC on a chiral stationary phase.

The results outlined above were obtained before carrying out the optimization of the reaction conditions for the  $\alpha,\beta$ -unsaturated nitriles described in section 6.2.1. Thus, it was decided to deploy the reaction conditions developed for  $\alpha,\beta$ -disubstituted acrylonitriles also to their  $\alpha,\beta$ -disubstituted analogs. To this end, (*E*)-2-methyl-3-phenylacrylonitrile ((*E*)-**6.72**) and (*Z*)-2-methyl-3-phenylacrylonitrile ((*Z*)-**6.73**) were subjected to the previously established conditions (table 6.21). Reduced reactivity and poor selectivity (*ee* up to 40%) were observed

in the hydrogenation of (**Z**)-**6.73**. The low enantioselectivity observed might be related to the isomerization of the C=C bond of the starting material under the reaction conditions. In fact, in the case of hydrogenations showing incomplete conversion, the unreacted acrylonitrile was detected as a mixture of (*E*)- and (*Z*)-isomer. Such an *in situ* isomerization could favor the coordination of the isomerized substrate to the metal center by the opposite enantioface and therefore might result in drastically reduced *ee* values.

**Table 6.21:** Hydrogenation of (*E*)-2-methyl-3-phenylacrylonitrile ((*E*)-**6.72**) or (*Z*)-2-methyl-3-phenylacrylonitrile ((*Z*)-**6.73**).

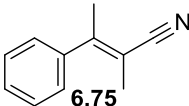
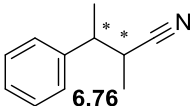
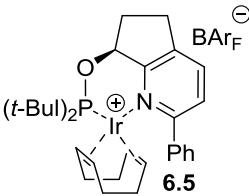
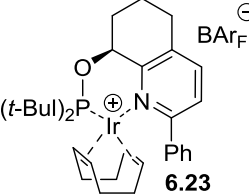
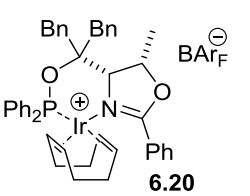
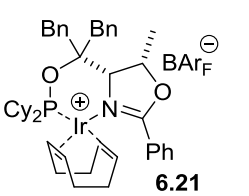
Catalyst	Substrate = ( <i>E</i> )- <b>6.72</b>			Substrate = ( <i>Z</i> )- <b>6.73</b>		
	Conv. [%] <sup>[a]</sup>	Isomerization [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>	Conv. [%] <sup>[a]</sup>	Isomerization [%] <sup>[a]</sup>	<i>ee</i> [%] <sup>[b]</sup>
	>99	--	5	>99	--	40
	96	21	n.d.	96	20	n.d.
	11	1	n.d.	35	--	20
	10	2	n.d.	9	--	rac

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

In order to fully test the applicability of this methodology, also the tetrasubstituted  $\alpha,\beta$ -unsaturated nitrile **6.75** was investigated as substrate in the asymmetric hydrogenation with

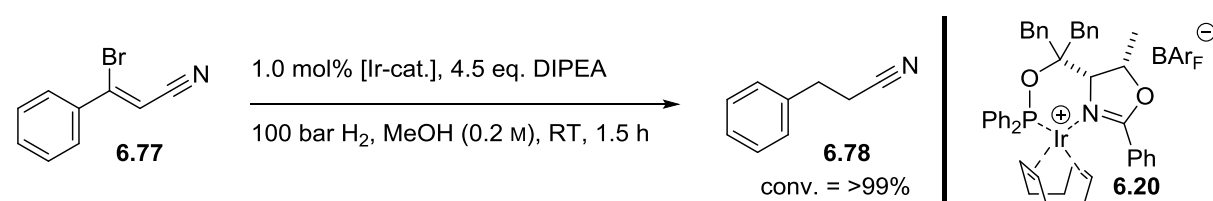
DIPEA as additive (table 6.22). Using the four complexes, which had been identified in the previous optimization of the reaction conditions as the most active and selective catalysts, only low conversion up to 6% was observed.

**Table 6.22:** Hydrogenation of the tetrasubstituted (*E*)-2-methyl-3-phenylbut-2-enenitrile (**6.75**).

 <b>6.75</b>	<div>1.0 mol% [Ir-cat.], 4.5 eq. DIPEA</div> <div>100 bar H<sub>2</sub>, MeOH (0.2 M), RT, 16 h</div>	 <b>6.76</b>	
 <b>6.5</b> conv. = 2% ee = n.d.	 <b>6.23</b> conv. = 3% ee = n.d.	 <b>6.20</b> conv. = 6% ee = n.d.	 <b>6.21</b> conv. = 1% ee = n.d.
Conversion determined by GC on an achiral stationary phase.			

Conversion determined by GC on an achiral stationary phase.

Finally, (*Z*)-3-bromo-3-phenylacrylonitrile (**6.77**), which was readily synthesized by the conversion of benzoylacetonitrile with phosphorus tribromide, was tested with catalyst **6.20**. Indeed, reduction of the C=C bond, but also cleavage of the C–Br bond was observed within 1.5 hours, leading to the unfunctionalized achiral nitrile **6.78** (scheme 6.7)



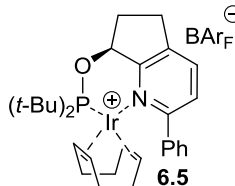
**Scheme 6.7:** (*Z*)-3-Bromo-3-phenylacrylonitrile (**6.77**) as substrate in the base-promoted hydrogenation.

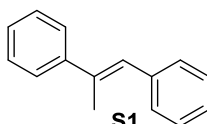
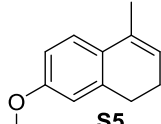
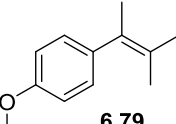
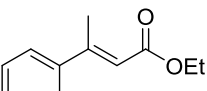
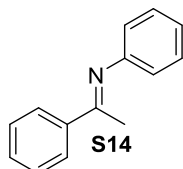
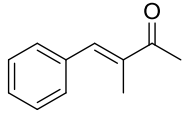
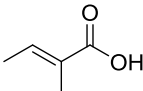
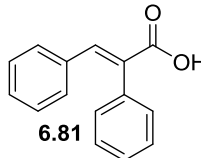
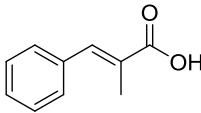
## 6.2.3 DIPEA as additive in the hydrogenation of other substrate classes

To investigate the scope of the base-activated catalysts system, substrates other than unsaturated nitriles were subjected to hydrogenation with DIPEA as additive and catalyst **6.5**. This iridium complex was chosen as it displayed some reactivity for both  $\beta,\beta$ -disubstituted and  $\alpha,\beta$ -disubstituted  $\alpha,\beta$ -unsaturated nitriles. As substrates, unfunctionalized olefins **S1**, **S5**, **6.79**,  $\alpha,\beta$ -unsaturated ester **S9**,  $\alpha,\beta$ -unsaturated ketone **S13**, prochiral imine **S14** and different  $\alpha,\beta$ -unsaturated carboxylic acids **6.81**, **6.82**, **6.83**, which have been successfully hydrogenated with Ir-complexes by Zhou and co-workers in the presence of a base,<sup>[36-37, 64a]</sup> were selected (table 6.23). In this series, reactivity was observed for the  $\alpha,\beta$ -unsaturated ester **S9** and the  $\alpha,\beta$ -unsaturated ketone **S13** but conversion remained below 25%. For all other substrates no conversion at all was registered.

**Table 6.23:** Hydrogenation of different substrates under base-promoted conditions.

$$\begin{array}{ccc}
 \begin{array}{c} R^2 \\ | \\ R^1-CH=CH-R^3 \end{array} & \xrightarrow[50 \text{ or } 100 \text{ bar } H_2, \text{ toluene (0.2 M), RT, 16 h}]{1.0 \text{ mol\% [Ir-cat.], 4,5 eq. DIPEA}} & \begin{array}{c} R^2 \\ | \\ R^1-CH^*-CH_2-R^3 \end{array}
 \end{array}$$

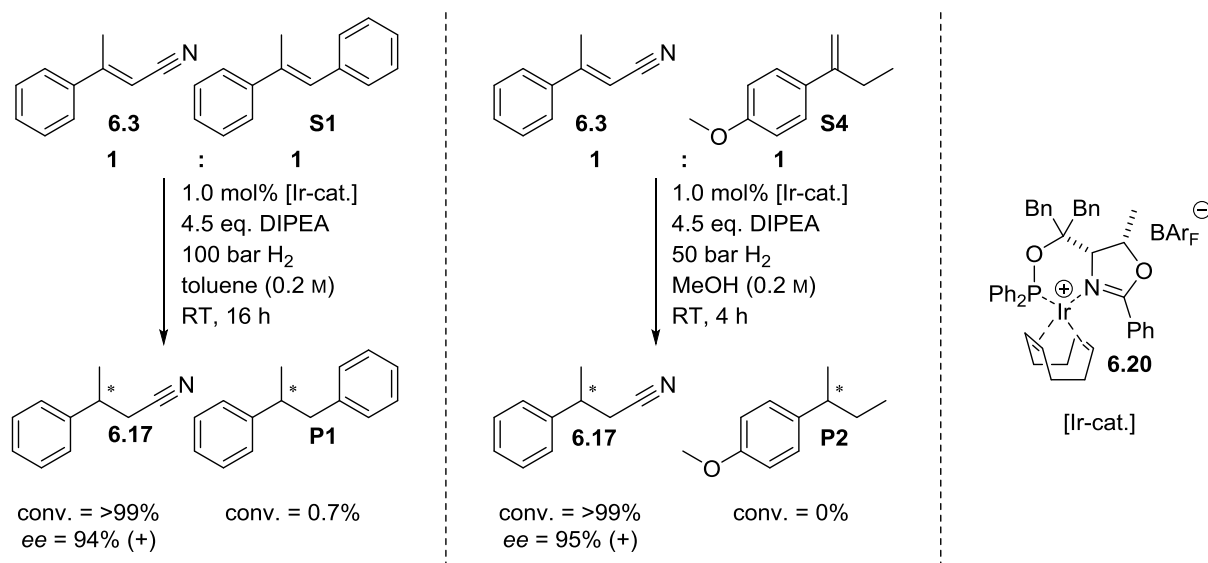

  
**6.5**

50 bar $H_2$	 <b>S1</b> conv. = 0%	 <b>S5</b> conv. = 0%	 <b>6.79</b> conv. = 0%	 <b>S9</b> conv. = 6% ee = 12% (S)	 <b>S14</b> conv. = 0%
100 bar $H_2$	 <b>S13</b> conv. = 23% ee = n.d.	 <b>6.80</b> conv. = 0%	 <b>6.81</b> conv. = 0%	 <b>6.82</b> conv. = 0%	

Conversion determined by GC on an achiral stationary phase.

These results indicate, that the cyano group is essential for catalytic activity under basic conditions. Therefore, control experiments were performed, where two unfunctionalized olefins were mixed in a one to one ratio with the  $\alpha,\beta$ -unsaturated nitrile **6.3** and subjected to hydrogenation conditions (scheme 6.8). Indeed, both tested substrates without a cyano group on the C=C bond showed no significant conversion, whereas the double bond of the  $\alpha,\beta$ -

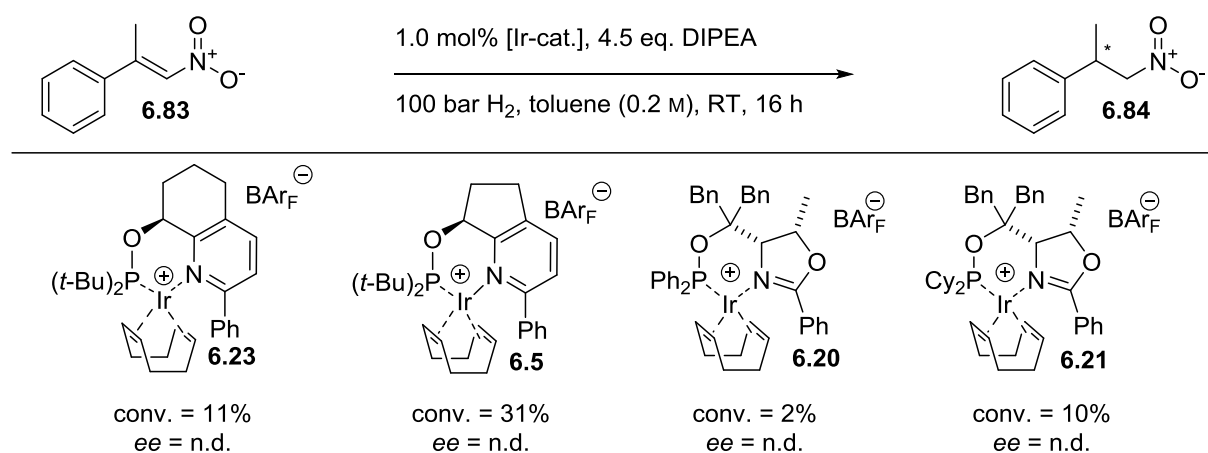
unsaturated nitrile **6.3** was reduced with full conversion and similar enantioselectivity as observed in the absence of another substrate.



**Scheme 6.8:** Hydrogenation of unfunctionalized olefins in the presence of (E)-3-phenylbut-2-enenitrile (**6.3**).

In order to further explore the applicability of the methodology, the  $\beta,\beta$ -disubstituted nitroalkene **6.83** was synthesized. This should represent a substrate class with a more electron deficient C=C bond (table 6.24). However, for this substrate only moderate reactivity with up to 31% conversion was observed. Furthermore, the order of reactivity of the tested catalysts changed notably compared to the hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3**.

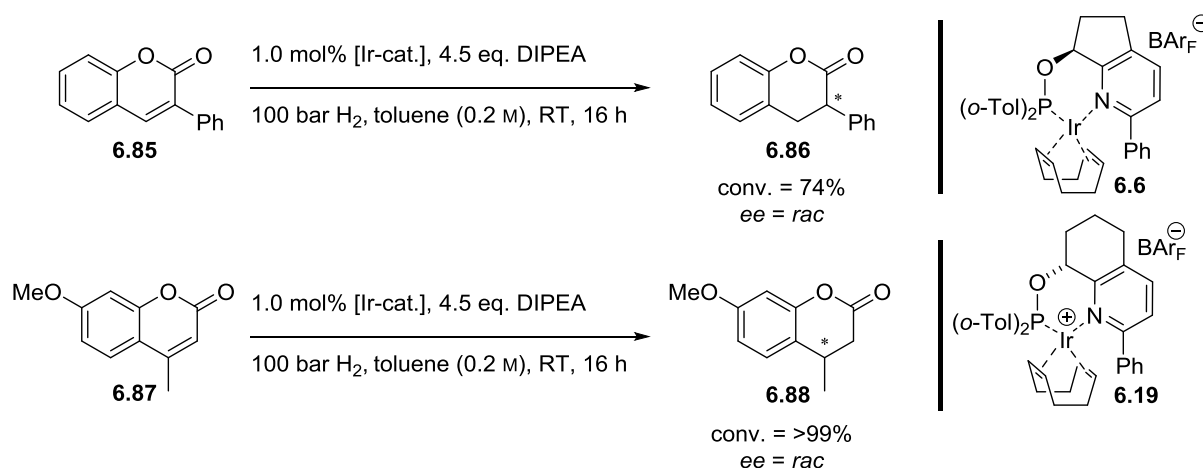
**Table 6.24:** Hydrogenation of (E)-(1-nitroprop-1-en-2-yl)benzene (**6.83**) under base-promoted conditions.



Conversion determined by GC on an achiral stationary phase.

Finally the two coumarin derivatives **6.85** and **6.87** were investigated. It should be noted, that for these substrates no reactivity under base free conditions was observed (see chapter 3).

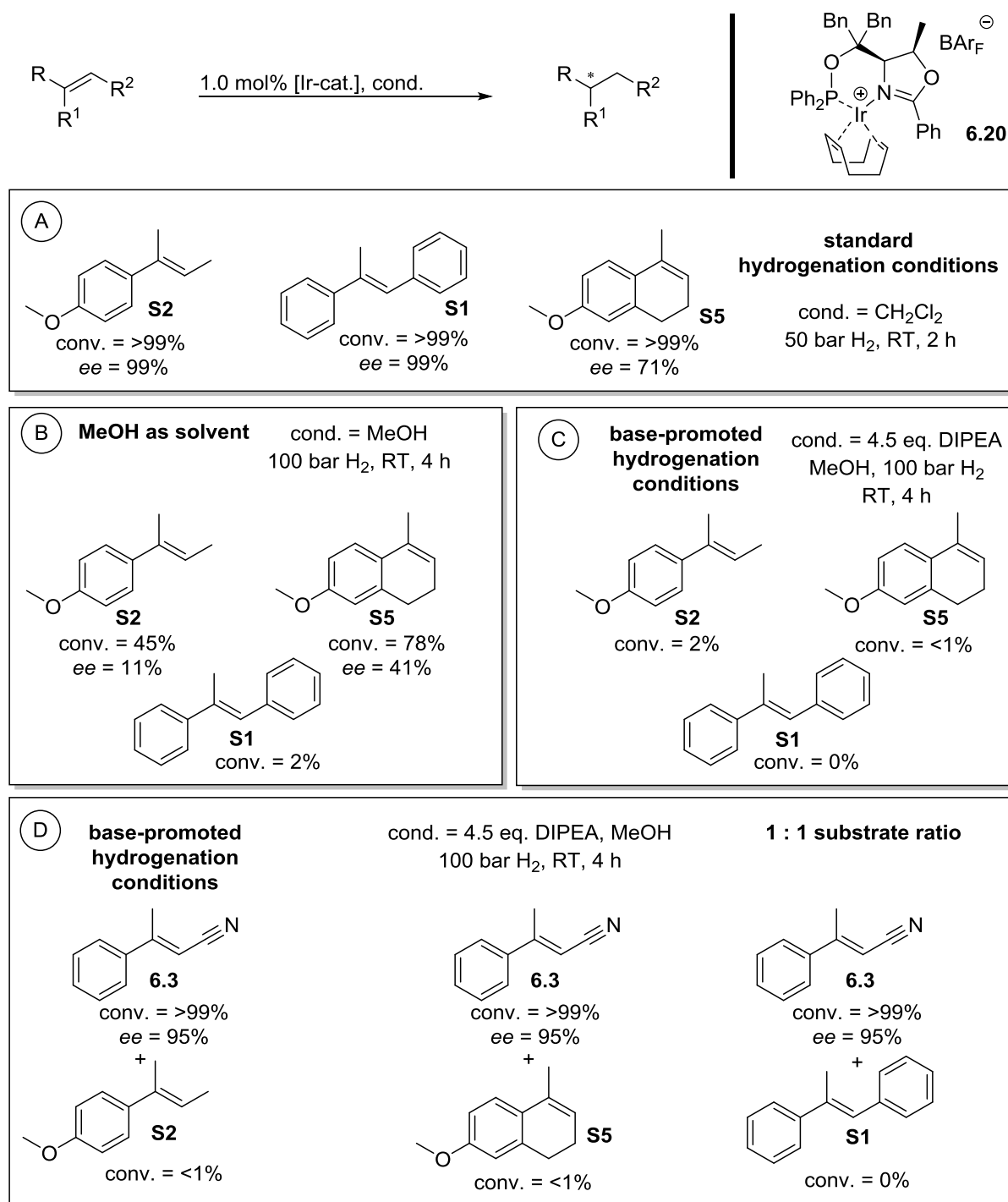
Indeed, addition of base resulted in increased reactivity and 74% and >99% conversion respectively were obtained (scheme 6.9). However, the products were racemic.



**Scheme 6.9:** Hydrogenation of the coumarin derivatives **6.85** and **6.87**.

In order to further explore why  $\alpha,\beta$ -unsaturated nitriles were hydrogenated with high enantioselectivity, whereas unfunctionalized olefins were not reduced under the same reaction conditions, a deeper investigation of the reaction parameters was performed. For example, applying catalyst **6.20** in the hydrogenation of the three selected unfunctionalized olefins under standard base-free reaction conditions, full conversion was observed for all of them (scheme 6.10, A).<sup>[28b]</sup> However, in MeOH, which gave excellent results in the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles, the reaction resulted in reduced conversions and considerably reduced enantioselectivity (scheme 6.10, B). Furthermore, by the addition of DIPEA catalyst **6.20** showed almost no reactivity (scheme 6.10, C). Hydrogenation of a 1:1 mixture of (*E*)-3-phenylbut-2-enenitrile (**6.3**) and the unfunctionalized olefin **S1**, **S2** or **S5**, less than 1% conversion was detected for all three unfunctionalized olefins. On the other hand the  $\alpha,\beta$ -unsaturated nitrile **6.3** was reduced with full conversion and with identical enantiomeric excess as in the absence of an unfunctionalized olefin (scheme 6.10, D). The observed chemoselectivity demonstrates the capability of this protocol to selectively reduce the C=C bond of an  $\alpha,\beta$ -unsaturated nitrile in the presence of other less electrophilic double bonds.

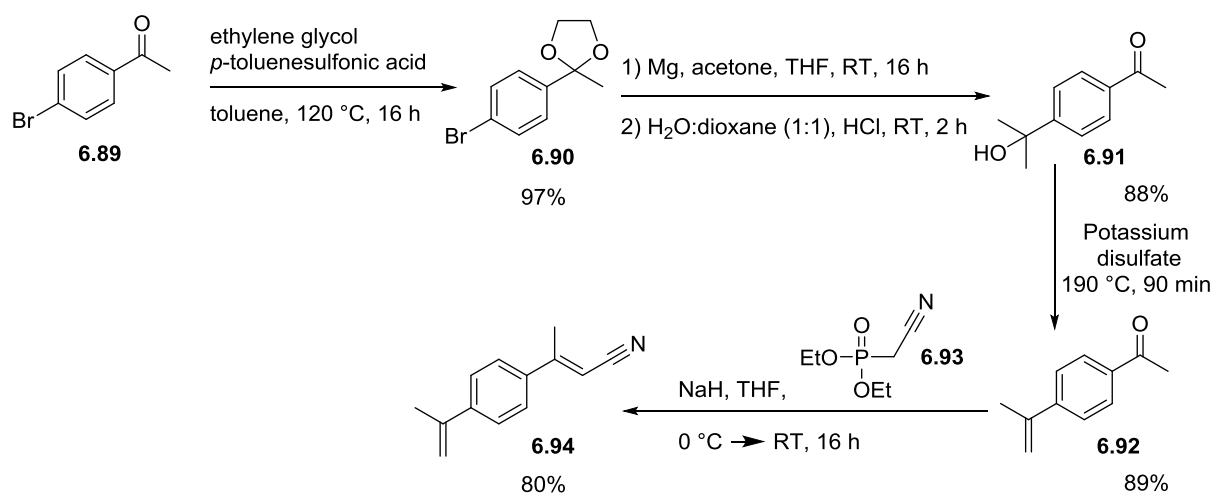




**Scheme 6.10:** Reactivity and selectivity studies of  $\alpha,\beta$ -unsaturated nitriles and unfunctionalized alkenes.

Since so far this chemoselectivity was demonstrated on intermolecular systems, it was of interest to test whether this protocol could also be successfully applied to  $\alpha,\beta$ -unsaturated nitriles containing an additional unfunctionalized C=C bond like **6.94**. The synthesis of compound **6.94** was accomplished by protection of 4'-bromoacetophenone (**6.89**), followed by Grignard addition to acetone and subsequent saponification of the acetal to afford the acetophenone derivative **6.91**. Elimination of the tertiary alcohol **6.91** followed by a Horner–

Wadsworth–Emmons reaction with ketone **6.92** resulted in the formation of the desired  $\alpha,\beta$ -unsaturated nitrile **6.94** in 4 steps and 61% overall yield (scheme 6.11).



**Scheme 6.11:** Synthesis of  $\alpha,\beta$ -unsaturated nitrile **6.94**.

Applying the substrate **6.94** in the Ir-catalyzed hydrogenation in the presence of DIPEA again a remarkably high chemoselectivity in favor of the double bond conjugated to the cyano group over the terminal C=C bond was observed. Under optimized conditions a ratio of 93.2 to 6.2 for the monohydrogenated product **6.95** was observed, with 96% *ee* for the major species (table 6.25, entry 11). This high chemoselectivity is remarkable considering the high reactivity of terminal C=C bonds under standard base-free conditions (1-(but-1-en-2-yl)-4-methoxybenzene, 1.0 mol% catalyst **6.20**, 0 °C, 1 bar H<sub>2</sub>, 30 min reaction time, full conversion).<sup>[28b]</sup>

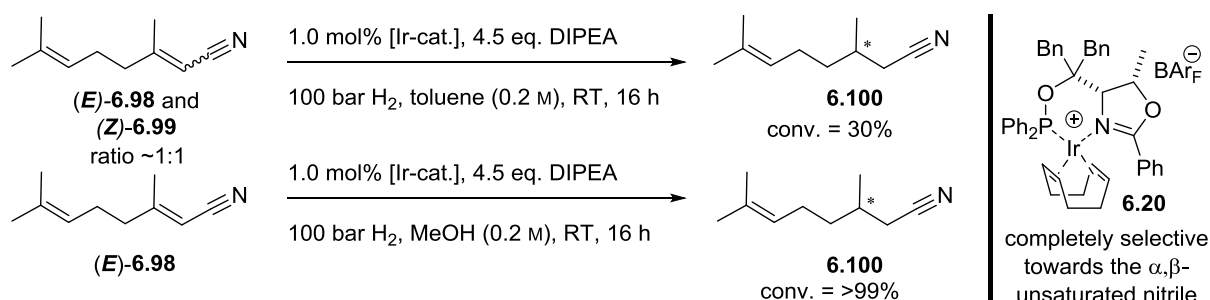
**Table 6.25:** Hydrogenation of the  $\alpha,\beta$ -unsaturated nitrile **6.94** containing an additional terminal double bond.

Entry	Cat.	Cat. [mol%]	solvent	T [°C]	<i>p</i> (H <sub>2</sub> ) [bar]	<b>6.95</b> [%]	<b>6.96</b> [%]	<b>6.97</b> [%]	<b>6.95</b> <i>ee</i> [%]
1 <sup>[a]</sup>		3.0	MeOH	25	100	44	18	18	n.d.

2 <sup>[a]</sup>		0.5	MeOH	25	50	84	0	4	n.d.
3 <sup>[a]</sup>		1.0	MeOH	25	100	71	0	29	n.d.
4 <sup>[a]</sup>		0.5	MeOH	25	50	77	0	23	n.d.
5 <sup>[a]</sup>		1.0	toluene	25	100	84	0	4	n.d.
6 <sup>[a]</sup>		1.0	CH <sub>3</sub> CN	25	100	91	0	4	96
7 <sup>[a]</sup>		0.5	MeOH	25	50	78	0	22	95
8 <sup>[b]</sup>		0.3	MeOH	25	100	71	0	29	87
9 <sup>[b]</sup>		0.2	MeOH	25	100	80	0	20	89
10 <sup>[b]</sup>		0.1	MeOH	25	100	87	0	13	88
11 <sup>[a]</sup>		1.0	MeOH	0	100	93.2	0	6.2	96

Conversion determined by GC on an achiral stationary phase. Enantiomeric excess determined by HPLC on a chiral stationary phase. [a] 4.5 eq. DIPEA were used; [b] DIPEA: 10 fold in terms of cat.-loading.

In order to further demonstrate the scope of this chemoselective hydrogenation method, an additional molecule containing two double bonds, geranyl nitrile was explored. In the hydrogenation of the commercially available (*E/Z*)-mixture (ratio ~1:1) 30% conversion in toluene with no preference for either the (*E*)- or the (*Z*)-isomer was observed (scheme 6.12). After separation of the (*E/Z*)-isomers by semi-preparative HPLC and hydrogenation in methanol full conversion to the mono-reduced nitrile **6.100** was observed starting from pure (*E*)-substrate **6.98**. In this case the unfunctionalized double bond remained completely untouched (scheme 6.12). Although no conditions for the determination of the enantiomeric excess were found, this example further demonstrates the high selectivity to reduce double bonds in conjugation to a cyano group by the use of this base-promoted protocol.

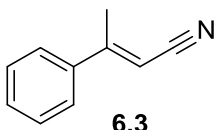
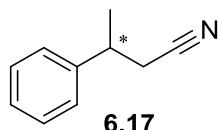
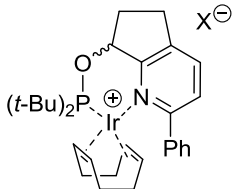
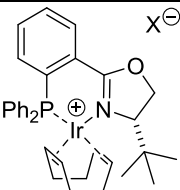


**Scheme 6.12:** Hydrogenation of geranyl nitrile under base-promoted conditions.

### 6.3 Influence of the counterion in base-promoted hydrogenations

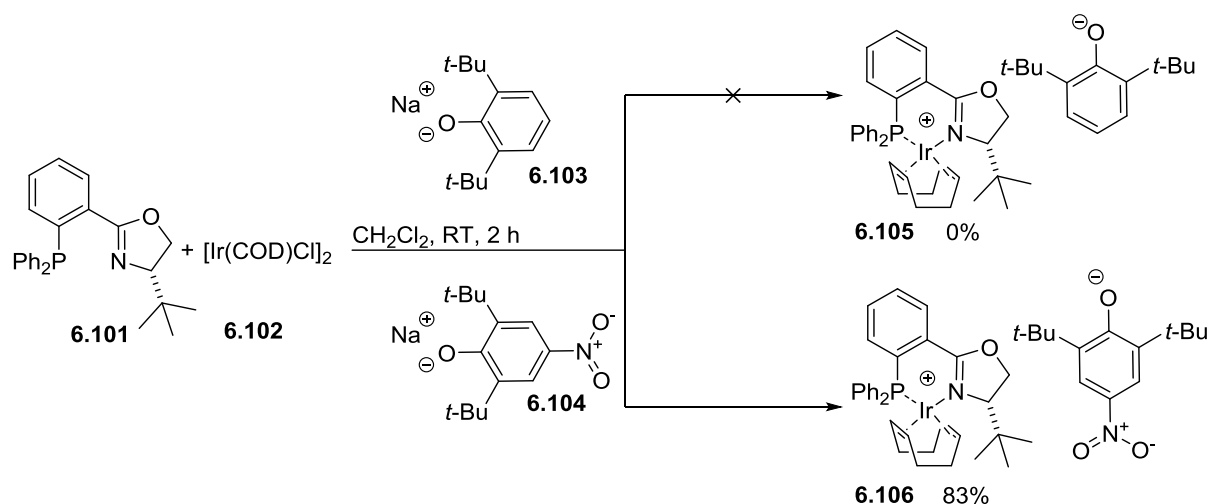
Next, the influence of the counterion was investigated.  $\text{BAr}_\text{F}$  emerged as the counterion of choice for iridium-based catalysts used in the hydrogenation of  $\text{C}=\text{C}$  bonds.<sup>[71a]</sup> As discussed in detail in chapter one,  $\text{BAr}_\text{F}$  as counterion was found to suppress the formation of catalytically inactive trinuclear Ir clusters, in contrast to more strongly coordinating counterions such as  $\text{PF}_6$ .<sup>[25]</sup> Therefore,  $\text{BAr}_\text{F}$  complexes display significantly higher catalytic activity and turnover numbers.<sup>[19]</sup> Furthermore iridium complexes are less sensitive to moisture and air. In fact, reactions usually can be set up under normal atmosphere without the need of specially dried solvents. Therefore,  $\text{BAr}_\text{F}$  salts of iridium complexes are considerably more robust and easier to handle, compared to their  $\text{PF}_6$ -analogs.<sup>[24]</sup> On the other hand, compared to  $\text{PF}_6$ , the  $\text{BAr}_\text{F}$  counterion is more expensive and has a higher molecular weight, that accounts for about one half of the overall weight of the catalyst. Therefore, the replacement of  $\text{BAr}_\text{F}$  as counterion with a less expensive, lighter anion would result in an less expensive catalysts with lower molecular weight. As the base-promoted Ir-catalyzed hydrogenation behaves differently compared to previously reported systems, the influence of the counterion was investigated by applying iridium complexes, with different counterions (table 6.26). Indeed, by comparing the same cationic complexes with  $\text{PF}_6$  and  $\text{BAr}_\text{F}$  as counterions, no difference in terms of catalytic activity and selectivity could be observed neither for catalyst **6.5** (entry 1 vs. 2) nor **6.12** (entry 3 vs. 4).

**Table 6.26:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3** with catalysts containing different counterions.

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p><b>6.3</b></p> </div> <div style="text-align: center;"> <p>1.0 mol% [Ir-cat.], 4.5 eq. DIPEA</p> <hr/> <p>100 bar <math>\text{H}_2</math>, MeOH (0.2 M), RT, 4 h</p> </div> <div style="text-align: center;">  <p><b>6.17</b></p> </div> </div>				
Entry	Catalyst	Counterion	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1		$\text{BAr}_\text{F}$	32	--
2 <sup>[c]</sup>		$\text{PF}_6$	32	--
3		$\text{BAr}_\text{F}$	13	21 (–)
4		$\text{PF}_6$	12	21 (–)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase; [c] Average value of two runs.

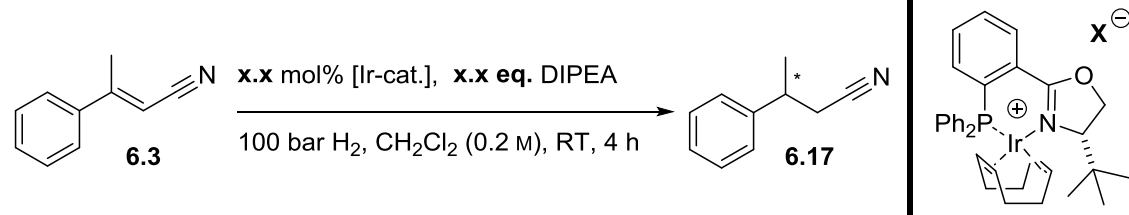
This observation suggested the possibility to design complexes with a completely different counterion, in order to tune the catalyst. A chloride would probably be the cheapest alternative but these complexes showed significantly reduced conversions. As just shown, the  $\text{PF}_6$  counterion gave no particular advantage in terms of reactivity when compared to  $\text{BAr}_\text{F}$ . Moreover, despite the lower cost of  $\text{PF}_6$ , the ThrePHOX catalyst **6.20** is commercially available as  $\text{BAr}_\text{F}$  complex and its conversion to the  $\text{PF}_6$  equivalent would have to bring appreciable advantage to justify its preparation and use. Therefore, the idea came up to use a basic counterion, which might overtake the role of DIPEA in the reaction. Hence, for exploratory studies conducted in this direction the applicability of 2,6-di-*tert*-butylphenolate **6.103**, which contains a sterically shielded oxygen atom, was investigated as counterion. However, all attempts to obtain the corresponding iridium complex **6.105** failed. The reaction mixture turned increasingly black and a black precipitate was collected, which could not be structurally characterized. Based on the observed color and the insolubility of the precipitate in organic solvents, most likely metallic iridium species was formed. Formation of metallic precipitates could be explained by the reduction of the Ir complex by the electron rich phenolate **6.103**. Therefore, the more electron deficient 2,6-di-*tert*-butyl-4-nitrophenolate **6.104** was tested, and indeed the desired complex **6.106** could be isolated in 83% yield (scheme 6.13).



**Scheme 6.13:** Synthesis of phenolate analogs of PHOX-iridium complexes.

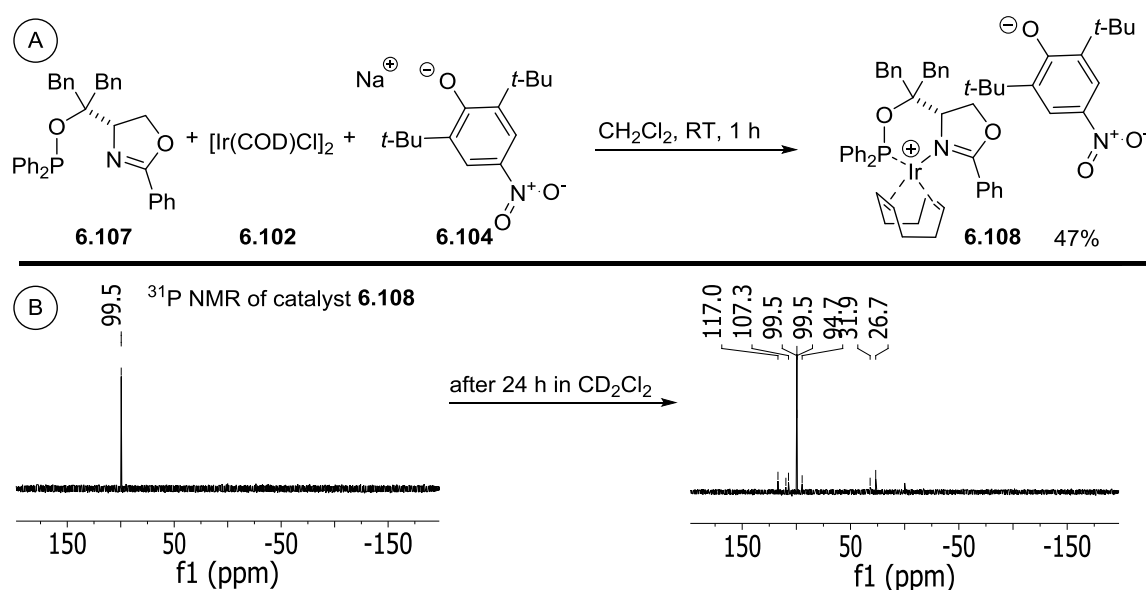
With this new catalyst in hand, its applicability to the hydrogenation of unsaturated nitrile **6.3** in the absence of DIPEA in  $\text{CH}_2\text{Cl}_2$  as solvent was tested. Indeed, this iridium phenolate complex **6.106** showed similar conversion and enantiomeric excess as observed with the  $\text{BAr}_\text{F}$ -analog of this catalyst with DIPEA as additive (table 6.27).

**Table 6.27:** Hydrogenation of  $\alpha,\beta$ -unsaturated nitrile **6.3**; comparison of  $\text{BAr}_\text{F}$  and 2,6-di-*tert*-butyl-4-nitrophenolate as counterion.

					
Entry	Catalyst loading [mol%]	DIPEA [eq.]	Counterion	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	1.0	4.5.	$\text{BAr}_\text{F}$	10	33 (–)
2	2.0	9.0	$\text{BAr}_\text{F}$	20	33 (–)
3	3.0	--	2,6-di- <i>tert</i> -butyl-4-nitrophenolate	28	32 (–)

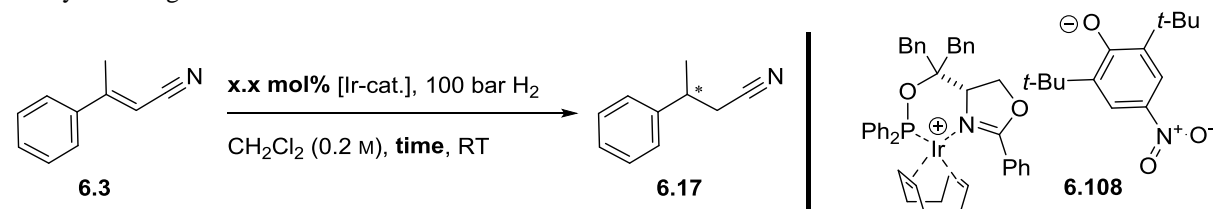
[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

Next, this concept was tested on a ligand complex which emerged to be more selective and reactive in the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles. Therefore, the SerPHOX complex bearing 2,6-di-*tert*-butyl-4-nitrophenolate as counterion was synthesized, for which the ligand was readily available in our group (scheme 6.14, A). The phenolate complex **6.108** was obtained in moderate yields and, in contrast to the previously described complex **6.106**, this catalyst turned out to be not stable for 24 h in  $\text{CD}_2\text{Cl}_2$  solution. The  $^{31}\text{P}$  NMR showed several new species and a considerable amount of precipitate was observed in the NMR tube (scheme 6.14, B).

**Scheme 6.14:** Synthesis of catalyst **6.108**, A;  $^{31}\text{P}$  NMR spectra of complex **6.108** after isolation and after 24 h in  $\text{CD}_2\text{Cl}_2$ , B.

Nevertheless, the applicability of this complex in the hydrogenation of various  $\alpha,\beta$ -unsaturated nitriles was tested. Comparing the results to those obtained with the  $\text{BAr}_\text{F}$  analog **6.20** and DIPEA similar selectivity was achieved (table 6.28). With 92% conversion at 0.2 mol% catalyst loading still high reactivity was observed although the maximum achievable turnover numbers are lower than with the DIPEA-modified catalyst system.

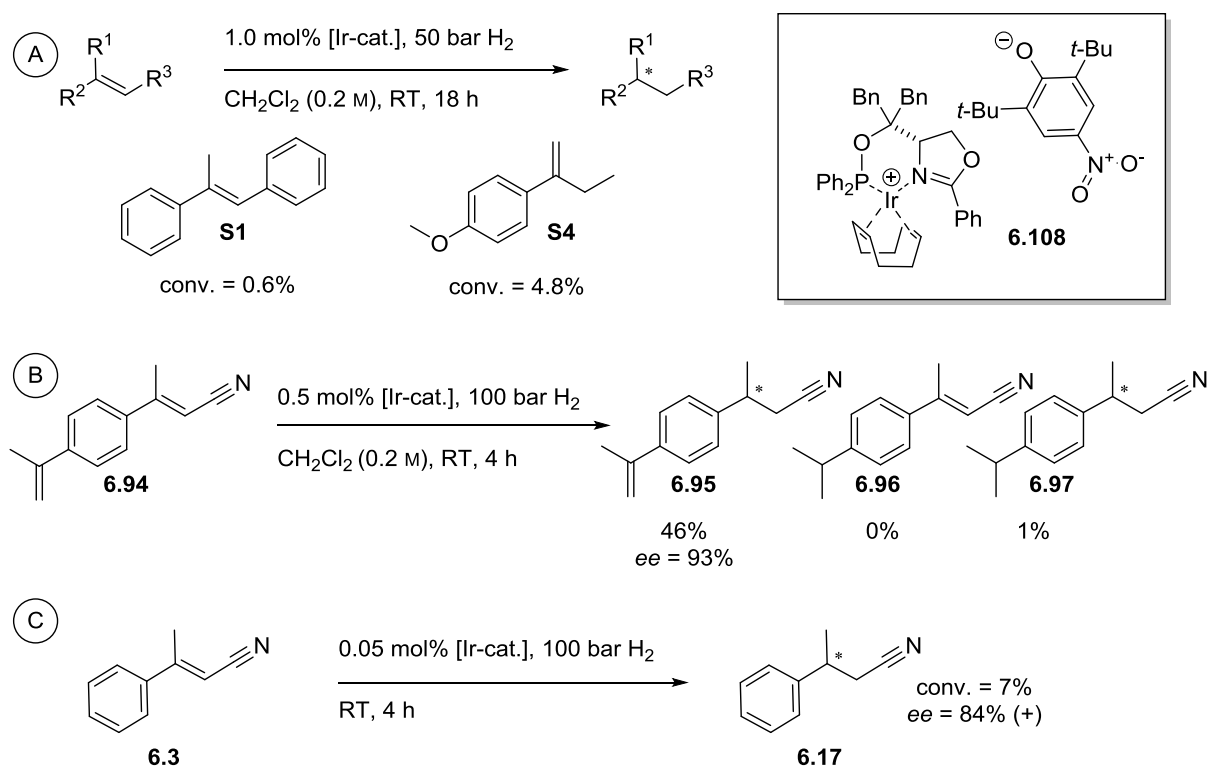
**Table 6.28:** Hydrogenations of  $\alpha,\beta$ -unsaturated nitrile **6.3** using iridium phenolate complex **6.106** at reduced catalyst loading.

				
Entry	Catalyst loading [mol%]	Time [h]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	1.0	4	>99	94 (+)
2	0.5	4	>99	94 (+)
3	0.2	4	92	92 (+)
4	0.1	4	31	95 (+)
5	0.05	16	4	95 (+)
6	0.05	72	7	94 (+)

[a] Determined by GC analysis on an achiral stationary phase; [b] Determined by HPLC on a chiral stationary phase.

In view of to the high catalytic activity of the phenolate complex, its applicability in the hydrogenation of unfunctionalized olefins was tested (scheme 6.15, A). By using 1 mol% catalyst loading, for *trans*-methylstilbene **S1** less than 1% conversion was obtained, whereas for the terminal olefin **S4** only 4.8% conversion was observed. Furthermore, the phenolate salt **6.108** showed high chemoselectivity in the hydrogenation of substrate **6.94**. Although only 47% conversion at 0.5 mol% catalyst loading was reached, the catalyst showed a high preference of 47:1 for the double bond conjugated to the cyano group (scheme 6.15, B). The newly synthesized phenolate complex **6.108** is soluble in the test substrate **6.3** and therefore the hydrogenation was performed without a solvent. At 0.05 mol% catalyst loading slightly higher conversion than in  $\text{CH}_2\text{Cl}_2$  was obtained, but the enantiomeric excess dropped to 84%

(scheme 6.15, C), close to the value which was observed performing the reaction in acetonitrile as solvent.



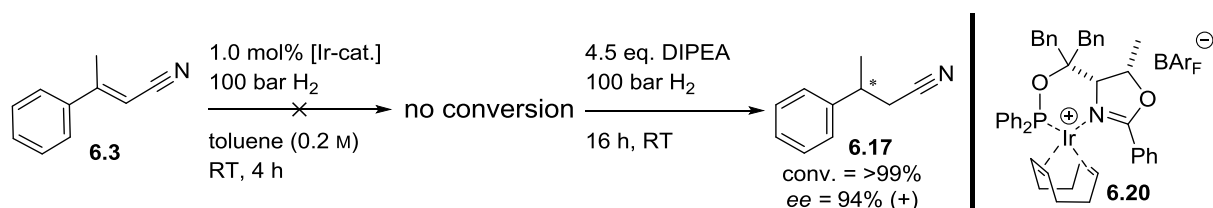
**Scheme 6.15:** Hydrogenations conducted with iridium complex **6.108**.



## 6.4 Mechanistic studies

The experimental observations obtained in the previous chapters indicate, that the base-modified catalyst system must operate through a different mechanism than under standard base-free conditions, for which the mechanism was discussed in chapter 1. Thus the question came up on the role of DIPEA, how it affects the reaction mechanism and whether mechanistic insight could be used to develop a more efficient catalyst system. The starting point for mechanistic studies was the iridium(III)-dihydride species **6.13** (scheme 6.5), which was isolated and characterized by standard analytical methods.

In order to check if the formation of iridium(III)-dihydride-dinitrile-species, such as **6.13**, is a dead-end of the catalytic cycle and if DIPEA as additive might avoid the formation of such a species, (*E*)-3-phenylbut-2-enenitrile (**6.3**) and catalyst **6.20** were subjected to hydrogenation conditions without DIPEA, to form the corresponding iridium(III) species of catalyst **6.20**. An aliquot was taken from the colorless reaction mixture, which revealed no conversion of the  $\alpha,\beta$ -unsaturated nitrile **6.3** after four hours. DIPEA was added and the reaction mixture was again subjected to the same hydrogenation conditions as before. Analysis of the reaction mixture 16 hours after addition of DIPEA revealed full conversion to the saturated nitrile **6.17** with the same enantiomeric excess, as when DIPEA was added before applying hydrogen pressure (scheme 6.16). Similar behavior was observed when the isolated PHOX-based iridium(III)-dihydride-dinitrile-species **6.13** was applied in the hydrogenation of the  $\alpha,\beta$ -unsaturated nitrile **6.3** in the presence of DIPEA. These results demonstrate that the active catalytic species can be generated from inactive iridium complexes, such as **6.13**.

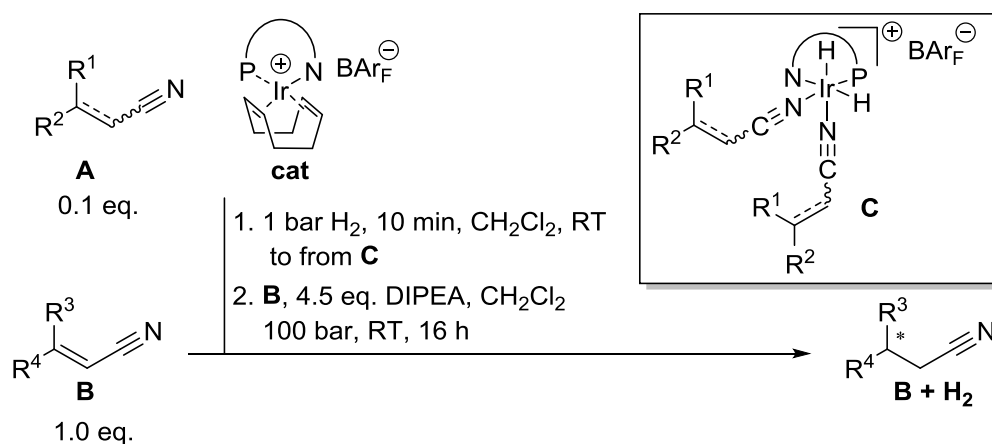


**Scheme 6.16:** Addition of DIPEA after the inhibition of the catalyst.

Based on the strong affinity of the cyano group to coordinate to the metal center, it was speculated that one substrate molecule might be bound during the enantioselectivity determining step to the metal center. In one scenario, one of the two substrate molecules which are coordinated to the metal center in pure CH<sub>2</sub>Cl<sub>2</sub> (**C**, scheme 6.17), might remain

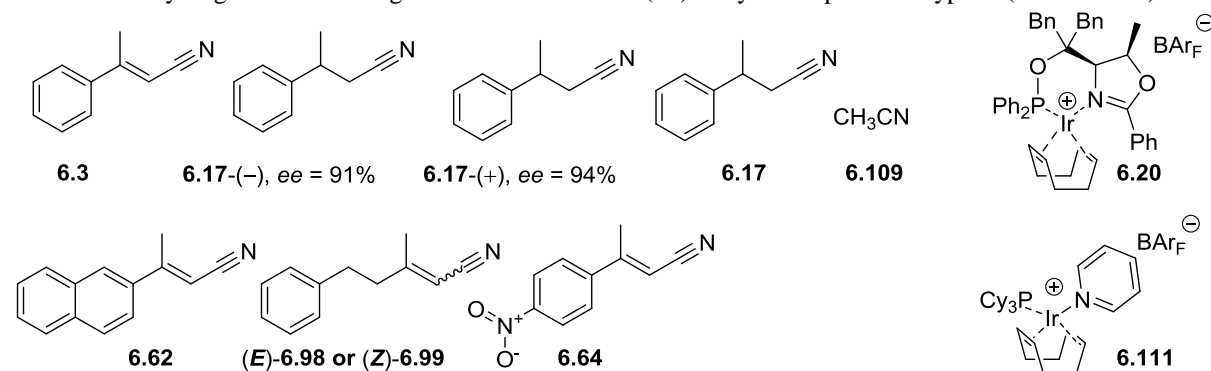
coordinated after the addition of base over the course of the reaction. In this case an influence on the enantiomeric excess and conversion could be expected. Therefore, the following experiments were performed (scheme 6.16).

First, a mixture of iridium complex (**cat**) and different nitriles (**A**) in a ratio of 1:10 was activated under weak pressure of  $H_2$  in  $CH_2Cl_2$ . During the activation period iridium(III)–dihydride-species of type **C** should be formed. Afterwards the desired substrate (**B**) and DIPEA were added and the reaction mixture was subjected to hydrogenation conditions (100 bar  $H_2$ ).



**Scheme 6.17:** Schematic diagram to illustrate the protocol applied to test for a coordination of a substrate during the enantioselectivity determining step.

In the different combinations of nitriles, substrates and catalysts tested no significant influence on the enantioselectivity was observed compared to the usual hydrogenation procedure (table 6.29, entry 1). The application of an achiral catalyst in combination with enantioenriched nitriles resulted in racemic samples (entry 5 and 6). When enantiopure catalysts were used only small differences in the enantioselectivity were observed. Such a small difference might also result from the different protocol applied. Furthermore, it was tested, if the conversion of substrate **6.64** might be increased with this “preactivation” of the catalyst (entry 11). But also in this case similar activity was observed. In light of these results, a coordination of a cyano group to the metal center during the enantioselectivity determining step cannot be excluded, but this assumption led not to the development a more efficient protocol for the base-promoted hydrogenation of  $\alpha,\beta$ -unsaturated nitriles.

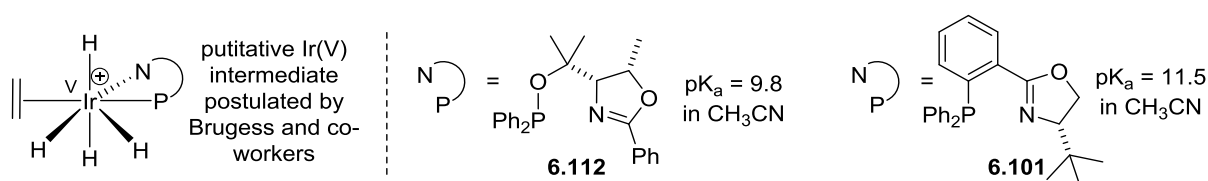
**Table 6.29:** Hydrogenations starting from different iridium(III)–dihydride-species of type C (scheme 6.16).

Entry	Cat.	Cat. loading [mol%]	A	B	Conv. (B) [%]	ee (B) [%]
1 <sup>[a]</sup>	6.20	0.5	--	6.62	>99	98 (+)
2 <sup>[a]</sup>	6.20	0.5	6.17	6.62	>99	95 (+)
3 <sup>[a]</sup>	6.20	0.5	6.17-(–)	6.62	>99	97 (+)
4 <sup>[a]</sup>	6.20	0.5	6.17-(+)	6.62	>99	97 (+)
5 <sup>[a]</sup>	6.111	3.0	6.17-(–)	6.62	>99	rac
6 <sup>[a]</sup>	6.101	3.0	6.17-(+)	6.62	>99	rac
7 <sup>[b]</sup>	6.20	1.0	6.17	(E)-6.98	>99	53 (+)
8 <sup>[b]</sup>	6.20	1.0	--	(E)-6.98	99	48 (+)
9 <sup>[b]</sup>	6.20	1.0	6.17	(Z)-6.99	>99	65 (–)
10 <sup>[b]</sup>	6.20	1.0	--	(Z)-6.99	>99	70 (–)
11 <sup>[a]</sup>	6.20	1.0	6.109	6.64	9	--
12 <sup>[a]</sup>	6.20	1.0	--	6.64	6	--

[a] Conversion determined by GC analysis on an achiral stationary phase; *ee* determined by HPLC on a chiral stationary phase; [b] Conversion and the *ee* determined by GC analysis on a chiral stationary phase.

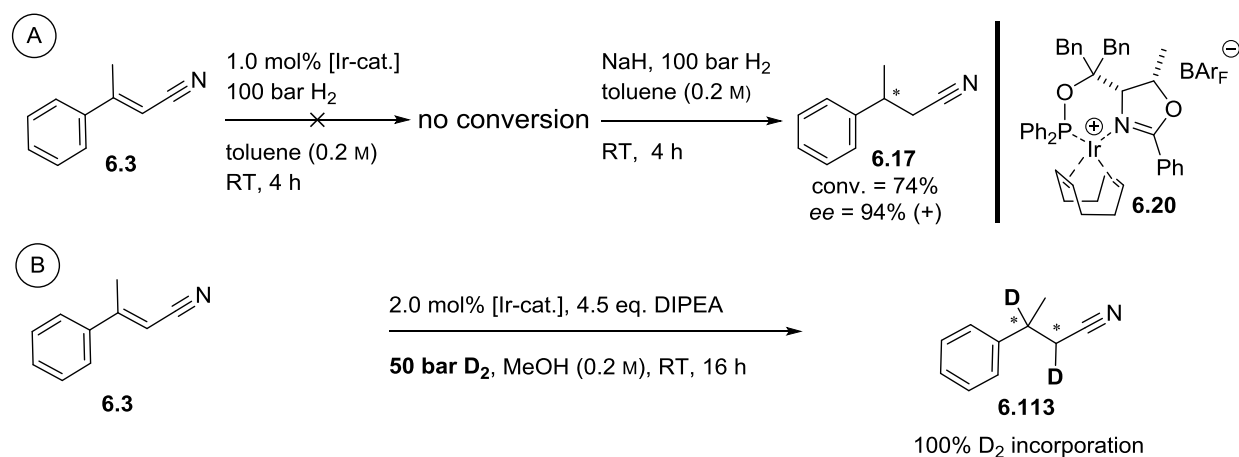
Based on a previously conducted experiments obtaining 70% conversion of the  $\alpha,\beta$ -unsaturated nitrile **6.3** with 0.1 eq. DIPEA in toluene (table 6.5, entry 7), a stoichiometric reaction of the base with the substrate can be excluded. Therefore, it is reasonable to assume a catalytic effect of the base. One possibility is a deprotonation step being involved in the

generation of the active catalytic species. As previously demonstrated, under hydrogen atmosphere the COD-ligand is reduced to cyclooctane and iridium(III)-dihydride-species, such as **6.13**, are formed.<sup>[113]</sup> Ir-hydrides of this type are known to be strong Brønsted acids.<sup>[41]</sup> Thus, the hydrides of such a iridium(III)-dihydride-species might be acidic enough to be deprotonated by DIPEA. Furthermore, starting from these intermediates it might be possible that iridium(V)-hydride species can be formed under hydrogen pressure, similar to those iridium(V)-hydride species postulated by Burgess and co-workers (figure 6.1). A  $pK_a$  of 9.8 in acetonitrile was calculated for such a putative intermediate for phosphinite-based ligand **6.112**.<sup>[41]</sup>



**Figure 6.1:** Acidity calculated by Burgess and co-workers for selected ligands on putative iridium(IV)-intermediates in hydrogenations.

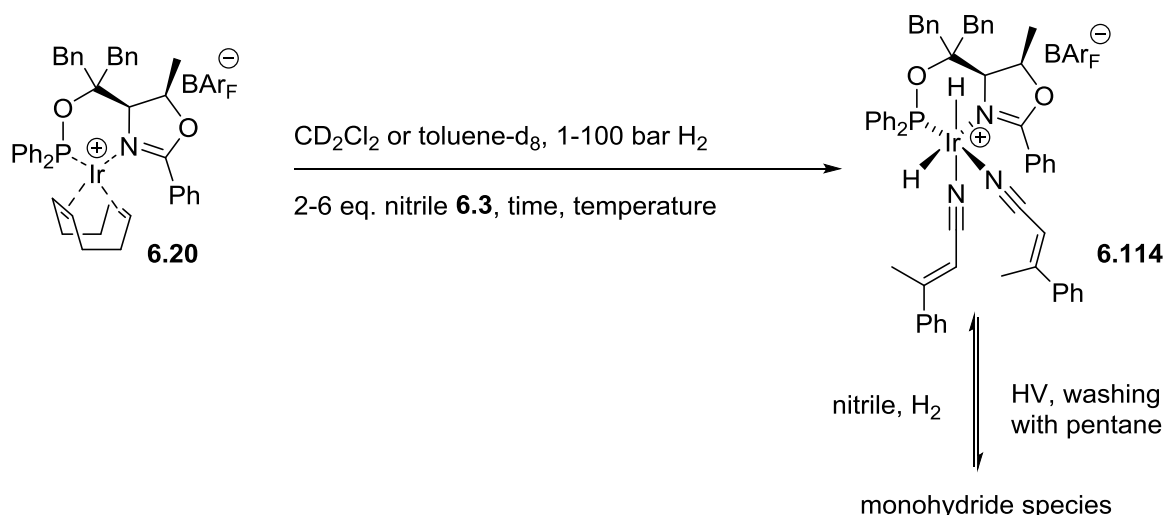
Hence, the activation of such iridium(III)-dihydride-species, such as **6.13**, was tested. In this case, instead of DIPEA sodium hydride was added to the reaction mixture. Also for this experiment 74% conversion to the saturated nitrile and 94% enantiomeric excess was observed (scheme 6.18, A). Therefore, the reaction can be triggered by a base without a potentially additional heteroatom. As next experiment a possible incorporation of protons from protic solvents such as methanol was investigated by a labeling study with deuterium gas. Such a incorporations might be a hint for a deprotonation step involved in the catalytic cycle which is not irreversible. As full incorporation of the deuterium in the final product was observed (scheme 6.17, C), proton transfer from solvent to catalyst can be ruled out.



**Scheme 6.18:** Several experiments conducted to gain an insight on the mechanism of this reaction.

Further investigations on iridium(III)-dihydride intermediates were performed in close collaboration with Dr. C. Kohrt during her two month PhD exchange within the research group of Prof. A. Pfaltz and are reported in this section (page 170 to 172) to reveal a complete picture of the mechanistic studies conducted in this project. The major goal of this study was to obtain the corresponding iridium(III)-dihydride-species of the most active catalysts and detect a deprotonation step starting from these intermediates. Therefore, the most selective catalyst **6.20** and the most reactive catalyst **6.23** were tested.

During careful investigation of different reaction conditions, which should lead to the isolation of the ThrePHOX-iridium(III)-dihydride species **6.114** it was found that the desired species could be obtained in solution. After removal of the solvent the <sup>1</sup>H NMR spectrum showed the signal of a monohydride, which could not be structurally characterized. However, after addition of nitrile **6.3** to a solution containing the mixture of the monohydride species and complex **6.114** under hydrogen atmosphere the monohydride species was converted to the dihydride-species **6.114** (scheme 6.19).

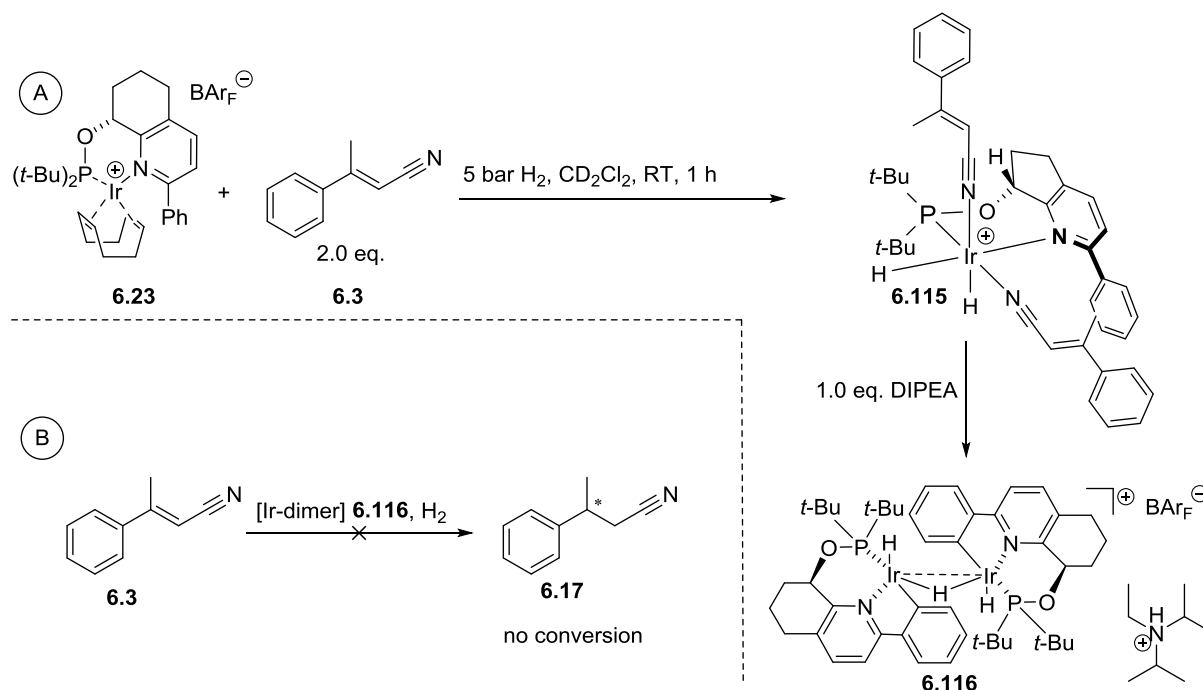


**Scheme 6.19:** Formation of the ThrePHOX-iridium(III)-dihydride species **6.114** and decomposition by the applied work-up.

Next, the behavior of catalyst **6.23**, which was the only catalyst that showed complete conversion at 1 bar hydrogen pressure, was investigated. Also this catalyst showed not such clean spectra as observed for the PHOX-based iridium complex **6.12**. In the case of catalyst **6.23** the  $^{31}\text{P}$  NMR spectra showed the formation of 2 different species in the presence of nitrile **6.3** under hydrogen atmosphere. By applying different reaction conditions it was possible to selectively isolate both species. The assignment of the identity of the first species was not possible with certainty. The second species was assigned to the expected iridium(III)-dihydride-species analogous to **6.115** of catalyst **6.23**. In this case, several hydride signals were observed. Furthermore, the  $^{31}\text{P}$  NMR spectra showed only one species. NMR experiments at  $-40\text{ }^\circ\text{C}$  resulted in a splitting of the phosphorus signal into 3 different peaks. By further NMR experiments, it was shown that the different hydride species are in exchange with each other and contain two different conformers of the expected dihydride-species **6.115** of catalyst **6.23**.

As next step, a possible deprotonation of the different dihydride species was investigated by adding different equivalents of DIPEA to the different dihydride species. For the PHOX derived iridium(III)-dihydride-species **6.13** no change in the NMR spectrum was observed. The addition of DIPEA to the iridium(III)-dihydride-species **6.114** of the ThrePHOX catalyst **6.20** resulted in the formation of many different species. Only the pyridine-based iridium(III)-dihydride-species **6.115** was converted in the presence of 1.0 eq. DIPEA into a single species (scheme 6.20). This compound was identified as the dinuclear complex **6.116** containing three hydrides and revealing a C–H insertion in each phenyl unit. This dinuclear complex was first observed by Dr. Andreas Schumacher in the context of diene reductions, and its structure was

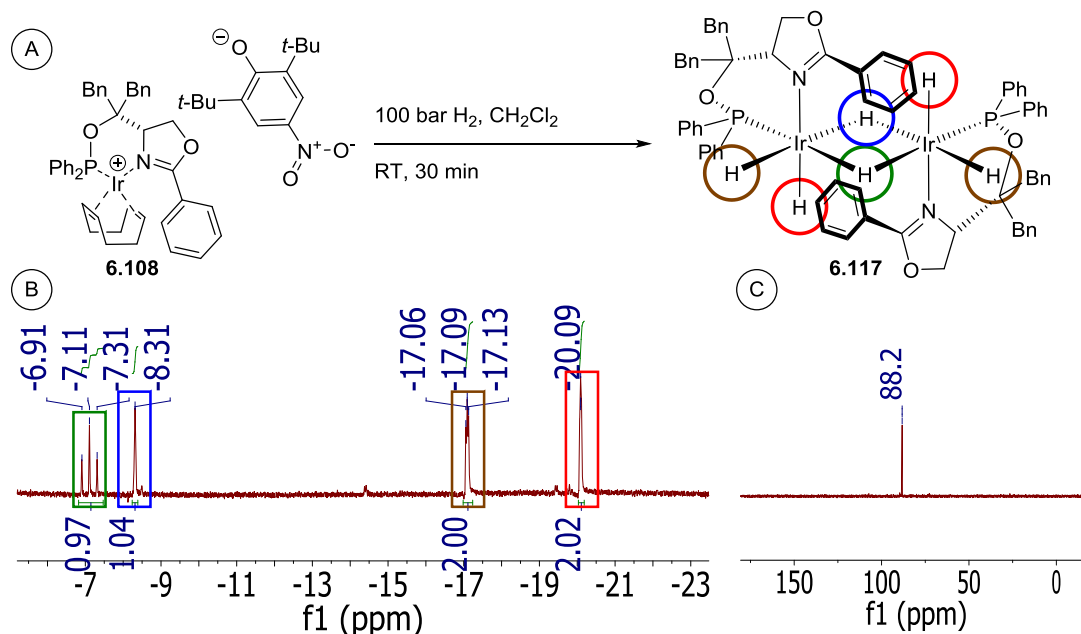
verified by single crystal X-ray analysis.<sup>[77]</sup> In hydrogenation experiments no reactivity of this dinuclear cluster for  $\alpha,\beta$ -unsaturated nitrile **6.3** was observed. Therefore, it can be considered as a dead-end of the catalytic cycle.



**Scheme 6.20:** Identification of the C–H inserted dinuclear cluster **6.116**, A; which showed no reactivity in the hydrogenation of the  $\alpha,\beta$ -unsaturated nitrile **6.3**, B.

All the experiments conducted so far did not lead to the identification of a deprotonation step involved in the catalytic cycle. In an attempt to demonstrate that such a deprotonation actually occurs, further studies using the SerPHOX-phenolate iridium complex **6.108** in the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles were conducted. In the case of this catalyst a perfect ratio of metal to base is predefined by its structure. Indeed, subjecting this catalyst to hydrogen atmosphere, the  $^{31}P$  NMR spectrum showed selective formation of only one new compound with a P signal at 88.2 ppm compared to 99.9 ppm for catalyst **6.108** (scheme 6.21). The  $^1H$  NMR spectrum revealed the formation of four new signals in the hydride region with a ratio of 1:1:2:2. One hydride as triplet at  $-7.02$  ppm with a coupling of 81 Hz, a singlet at  $-8.23$  ppm, a multiplet at  $-17.00$  ppm and a singlet at  $-19.99$  ppm. Based on NMR spectroscopy, the structure of this species was assigned to the  $C_2$  symmetric dinuclear iridium species **6.117** bearing two bridging hydrides. One of these hydrides is located *trans* to two phosphorus atoms resulting in the triplet with 81 Hz coupling (green). The other bridged hydride with an integral of one occurs as singlet at  $-8.31$  ppm (blue). The signals with an integral of two belong to two pairs of terminal hydrides. The first pair of

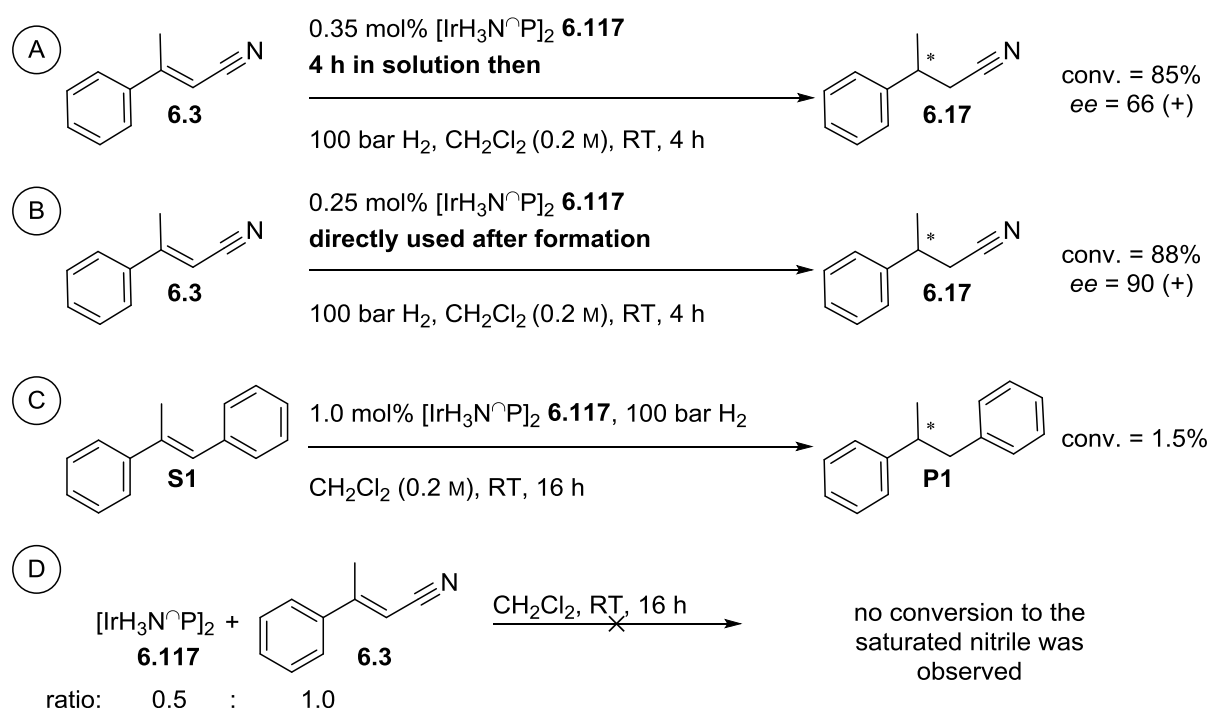
terminal hydrides (red) is located in axial position *trans* to a nitrogen atom and on the opposite side of the plane defined by the two iridium atoms and the two bridging hydrides. The other pair (brown) is found in the plane defined by the two iridium atoms and the two bridging hydrides. Overall this complex is neutral and the shift of the obtained hydrides is similar to a neutral dinuclear complex of this geometry observed for hemilabile pincer ligands described by Gusev and co-workers.<sup>[121]</sup>



**Scheme 6.21:** Observed dimeric species **6.117** after applying hydrogen atmosphere to complex **6.108**, A; hydride region of the  $^1\text{H}$  NMR spectrum, B;  $^{31}\text{P}$  NMR spectrum, C.

With this dinuclear iridium complex in hand, several hydrogenations were performed. First, the dinuclear iridium complex **6.117** was applied as catalyst in the hydrogenation of the  $\alpha,\beta$ -unsaturated nitrile **6.3**. It was found that significantly different results were obtained depending on the handling of the dinuclear iridium complex **6.117**. Significantly reduced conversion and selectivity compared to hydrogenations by the phenolate complex **6.108** were observed when the dinuclear iridium complex **6.117** was stored for 4 h under inert conditions in solution (scheme 6.22, A). If dimer **6.117** was used directly after formation, the reaction gave 88% conversion and 90% *ee*, similar to the results obtained with phenolate complex **6.108**. Furthermore, complex **6.117** showed only 1.5% conversion in the hydrogenation of the stilbene **S1** with 2.0 mol% catalyst based on iridium. Taking into account that complex **6.117** already contains six hydrides, the question came up if it can be used as a stoichiometric hydrogenation reagent. Unfortunately, no conversion was obtained by stirring the hexahydride-dimer **6.117** in the presence of the  $\alpha,\beta$ -unsaturated nitrile **6.3**.





**Scheme 6.22:** Several experiments conducted with the dinuclear iridium complex **6.117**.

Although it was not possible to demonstrate the occurrence of a deprotonation step in the base-promoted hydrogenation of the  $\alpha,\beta$ -unsaturated nitriles, several experiments support this hypothesis. A neutral iridium hydride complex formed by a deprotonation would be expected to be less electrophilic and, consequently, release a bound nitrile more easily, opening up a free coordination site, which is required for the reaction. Moreover, the hydride would be more nucleophilic than hydrides in a cationic dihydride complex, facilitating hydride transfer to the electrophilic C=C bond of an  $\alpha,\beta$ -unsaturated nitrile.

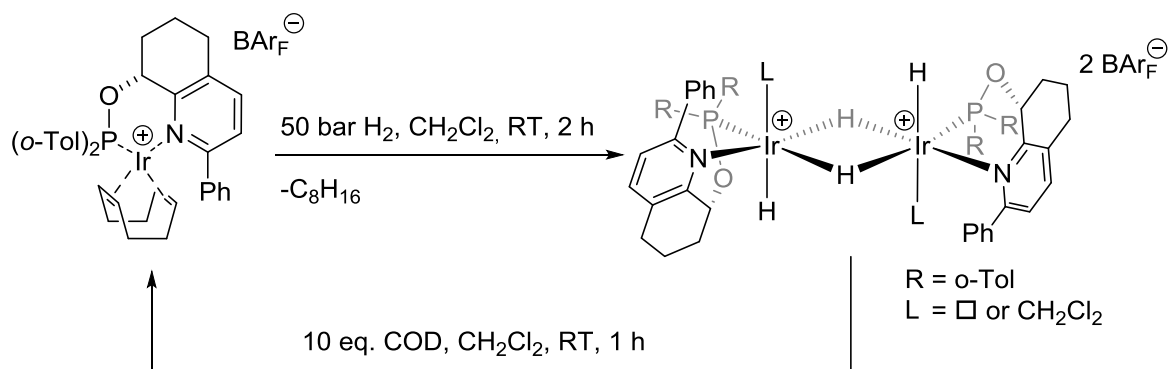
## 6.5 Conclusion

In summary, it was found that addition of an external sterically hindered amine base or the presence of a basic counterion in the catalyst dramatically enhance the catalytic activity of iridium N,P ligand complexes in the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles. While these catalysts show no reactivity towards  $\alpha,\beta$ -unsaturated nitriles under base-free conditions, the base-activated catalyst systems allow smooth hydrogenation at low catalyst loadings, affording the corresponding saturated nitriles with high conversion and excellent enantioselectivity. In contrast, other alkenes lacking a conjugated cyano group do not react

under these conditions. So it becomes possible to selectively reduce the cyano-substituted C=C bond of an  $\alpha,\beta$ -unsaturated nitrile, leaving other types of C=C bonds in the molecule intact. Thus the catalyst systems described herein enable enantio- and chemoselective hydrogenations, for which no suitable catalysts were available before.

# Chapter 7

## Recovery of Iridium-Based N,P Ligand Complexes after Hydrogenation Reactions



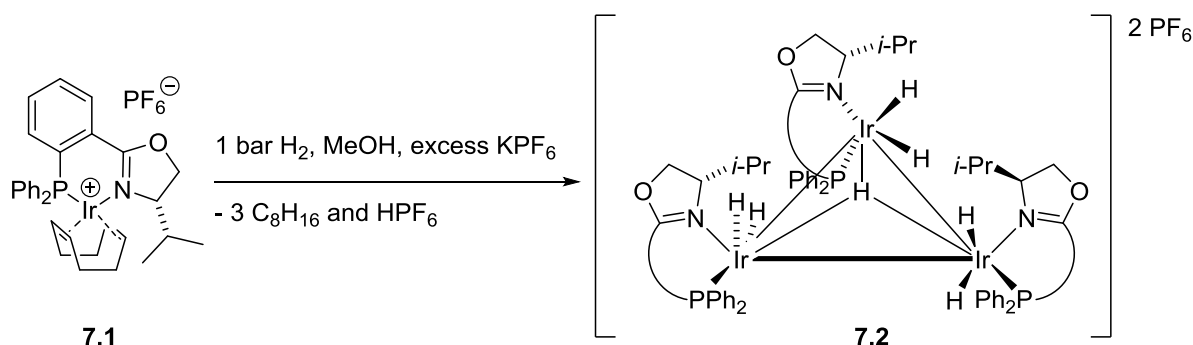
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## 7.1 Introduction

As demonstrated in the previous chapters, the asymmetric hydrogenation with iridium N,P ligand complexes has emerged as an efficient tool for the introduction of stereogenic centers starting from prochiral olefins. Although, when compared to other catalysts based on Ru and Rh, they have found more limited application,<sup>[11b]</sup> this is mainly due to the fact that Rh- and Ru-based catalyst have been investigated since long before the first successful application of chiral iridium-based N,P ligand complexes was reported in 1998.<sup>[19]</sup> In addition, iridium-based catalysts normally do not achieve high turnover numbers, as those that can be reached by Rh- or Ru-based systems in the hydrogenation of prochiral alkenes. Furthermore, for those catalysts the mechanism is well understood.<sup>[122]</sup> For iridium-based systems, many experiments and calculations have been conducted, based on Ir<sup>I/III</sup> or Ir<sup>III/V</sup> catalytic cycles proposing different pathways, but on the obtained data it is difficult to draw a definite conclusion at this point.<sup>[46, 123]</sup>

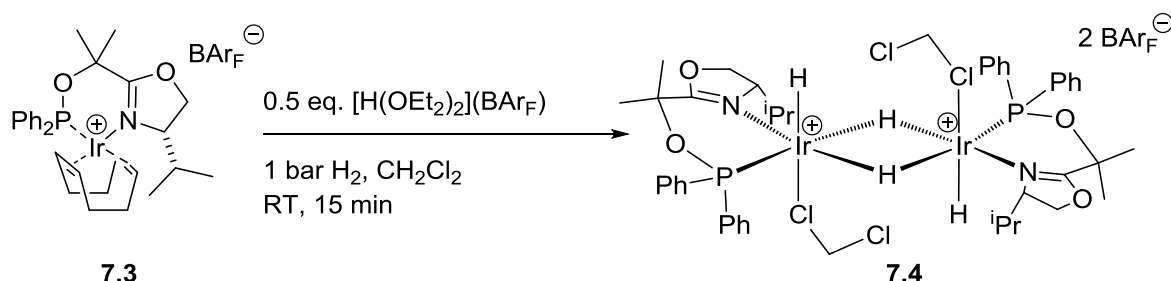
A fundamental impact on the design of more reactive and stable catalysts is based on the understanding of the catalytic cycle, but also the elucidation of decomposition pathways, generating catalytically inactive or less stereoselective species, plays a crucial role. In this context, it was demonstrated in previous studies that iridium-based catalysts bearing monodentate N and P ligands, such as [Ir(COD)(PCy<sub>3</sub>)(py)]PF<sub>6</sub>, form trimeric and tetrameric iridium hydride clusters under hydrogenation conditions.<sup>[26, 124]</sup> This behavior was also observed for iridium-based catalyst **7.1** bearing a chiral bidentate N,P ligand. Upon treatment of [Ir(COD)(PHOX)]PF<sub>6</sub> **7.1** with hydrogen, the formation of the trinuclear cluster **7.2** was observed (scheme 7.1).<sup>[25]</sup>



**Scheme 7.1:** Formation of the catalytically inactive trinuclear cluster **7.2**.

All of these iridium polyhydride clusters are inactive as hydrogenation catalysts and all efforts to convert the trinuclear cluster **7.2** into an active catalytic species were not unsuccessful, so far.<sup>[25]</sup> Therefore, the formation of these clusters reveals a pathway whose understanding and suppression should result in the development of more efficient hydrogenation processes.

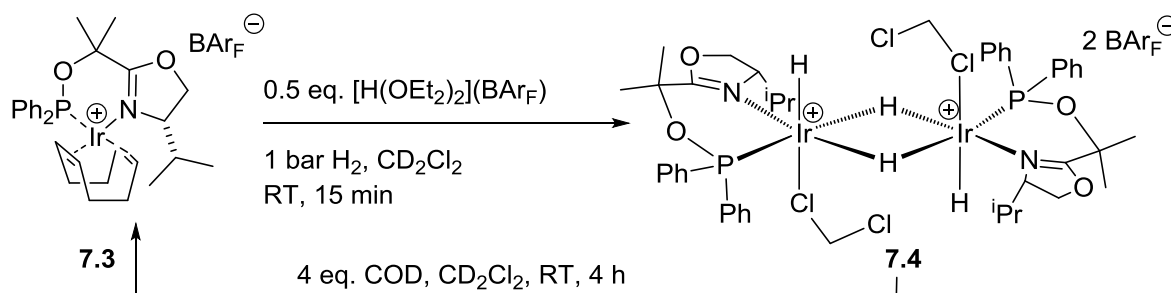
Recent studies facing this issue were conducted in our research group by Dr. Stefan Gruber.<sup>[125]</sup> In the course of his investigations it was found that Ir-SimplePHOX catalyst **7.3** is converted almost quantitatively (>95%) to dimeric Ir-hydride complex **7.4** in the presence of  $[\text{H}(\text{OEt}_2)_2]\text{BAR}_\text{F}$  (scheme 7.2).



**Scheme 7.2:** Dimeric Ir-hydride complex **7.4** obtained in the presence of  $[\text{H}(\text{OEt}_2)_2]\text{BAR}_\text{F}$ .

$[\text{H}(\text{OEt}_2)_2](\text{BAR}_\text{F})$  was employed as acidic additive to suppress the formation of the corresponding trinuclear complex which needs the liberation of a proton (see scheme 7.1). When the reaction was repeated in the absence of  $[\text{H}(\text{OEt}_2)_2](\text{BAR}_\text{F})$ , the formation of ~20% of corresponding trinuclear complex of this type as **7.2** was observed by  $^1\text{H}$  NMR under otherwise identical reaction conditions.

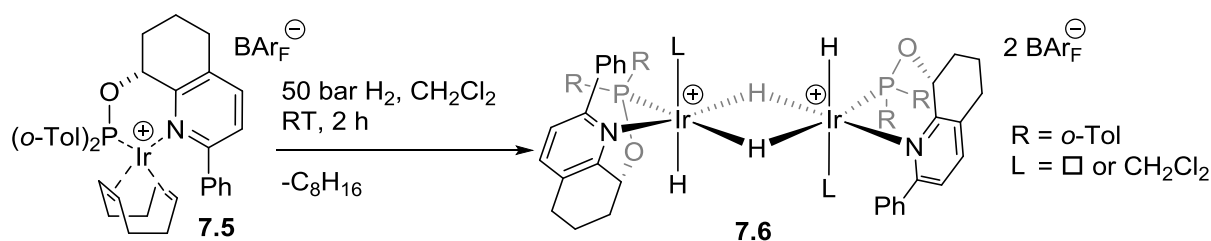
Further, it was shown during this study that by the addition of acetonitrile it is possible to break up dinuclear clusters like **7.4**. This behavior was not observed while stirring the trinuclear clusters **7.2** in the presence of acetonitrile. In addition, the dinuclear clusters described by Dr. Stefan Gruber showed notable catalytic reactivity in the hydrogenation of unfunctionalized olefins. Such observations led to the assumption that dinuclear clusters can be split by olefins and to go one step further, also by the addition of 1,5-cyclooctadiene (COD) to regenerate the precatalyst used in the asymmetric hydrogenation. Indeed, by the addition of COD to the dimer **7.4**, complete and clean regeneration of catalyst **7.3** was achieved (scheme 7.3). Further to these results, efforts were made in collaboration with Dr. Stefan Gruber to establish a method for the recovery of Ir catalysts from reaction mixtures. Results of such investigations are discussed in this chapter.



**Scheme 7.3:** Quantitative recovery of catalyst **7.3** by the addition of COD.

## 7.2 Formation of dimeric iridium complexes in solution

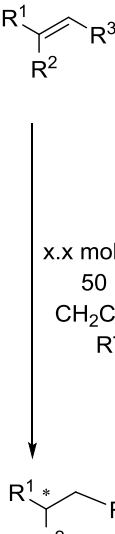
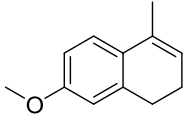
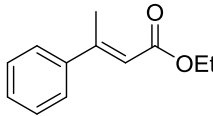
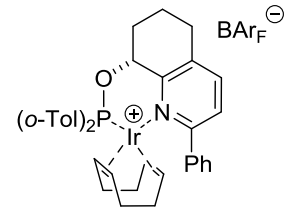
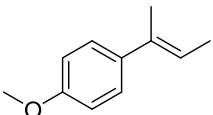
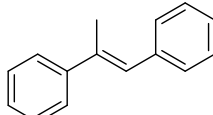
The above observation led to the idea that it should be possible to suppress the formation of trimers during the hydrogenation reaction by the addition of an acid, such as  $[\text{H}(\text{OEt}_2)_2]\text{BAr}_\text{F}$ . However, even the addition of a catalytic amount of  $[\text{H}(\text{OEt}_2)_2]\text{BAr}_\text{F}$  had a detrimental effect on the reactivity and selectivity of the hydrogenation reaction.<sup>[125]</sup> To explore the applicability of this concept, the behavior of different catalysts under hydrogen pressure in the absence of substrate was investigated. The goal was to get an insight on how fast and to what extent dimeric and trinuclear iridium complexes were formed. At first, the pyridine-based catalyst **7.5** was considered, as it shows high efficiency in the hydrogenation of tocopherol side-chain precursors and  $\gamma$ -tocotrienyl acetate (see chapter 4),<sup>[53b, 53c, 126]</sup> and therefore is at the moment the most promising candidate for a possible industrial application. Moreover, the synthesis of this catalyst is rather laborious and hence represents one of the most interesting candidates for recovery of the catalyst. Therefore, NMR studies were conducted to gain a first impression on how this catalyst reacts in the absence of a substrate under hydrogen pressure. Hence, catalyst **7.5** was dissolved in  $\text{CD}_2\text{Cl}_2$  and stirred under 50 bar hydrogen pressure for 2 h (scheme 7.4). Interestingly, the NMR spectra revealed the formation of almost exclusively one species. Also after longer reaction times under a hydrogen atmosphere no significant decomposition of this species or conversion to a polynuclear cluster could be detected. After evaluation of the NMR spectra, the species could be assigned as the dinuclear iridium hydride complex **7.6**, bearing in total four hydrides, two bridging hydrides and one on each metal center in axial position on the opposite side of the  $\text{Ir}_2(\mu\text{-H})_2$  plane. The *anti* orientation of the two phosphinite units confers a  $C_2$  symmetry to the dimer, with the rotation axis through the two bridging hydrides. Only small amounts (<5%) of different hydride species were formed. However, it was found by NOE experiments that these species are in exchange with the dimer in its major conformation.



**Scheme 7.4:** Formation of the new dinuclear hydride complex **7.6** from catalyst **7.5** ( $\square$  refers to a vacant coordination site).

With this result in hand, the behavior of the dimer **7.6** was further investigated. In particular, it was interesting to ascertain whether such dimer could be reconverted to the precatalyst **7.5** by addition of COD, whether it would be catalytically active and how would it react upon addition of a substrate. First, the isolation of the dimer **7.6** by simple evaporation of the solvent was tested. Indeed, the dimer could be isolated when carefully handled under an argon atmosphere and only slow decomposition was observed by storing it at  $-25\text{ }^{\circ}\text{C}$  under an inert atmosphere. This allowed us to compare the catalytic behavior of dimer **7.6** and its precursor complex **7.5** (table 7.1). The comparison of both metal complexes showed a somewhat higher reactivity for the metal complex bearing the COD ligand **7.5**. Only *trans*- $\alpha$ -methylstilbene **S1**, showed similar low conversion. The enantiomeric excesses induced by the dimer **7.6** and its precursor catalyst **7.5**, were identical.

**Table 7.1:** Comparison of catalyst **7.5** and dimer **7.6** in the hydrogenation of selected substrates.

	 <p><b>S5</b> 1.0 mol% based on Ir [Ir-cat.] <b>7.5</b> conv. = &gt;99%, ee = 92% (S) [Ir-cat.] <b>7.6</b> conv. = &gt;99%, ee = 92% (S)</p>		 <p><b>S9</b> 0.4 mol% based on Ir [Ir-cat.] <b>7.5</b> conv. = 8%, ee = n.d. [Ir-cat.] <b>7.6</b> conv. = 3%, ee = n.d.</p>		 <p><b>7.5</b></p>
	 <p><b>S2</b> 0.4 mol% based on Ir [Ir-cat.] <b>7.5</b> conv. = &gt;99%, ee = 99% (R) [Ir-cat.] <b>7.6</b> conv. = 76%, ee = 99% (R)</p>		 <p><b>S1</b> 0.4 mol% based on Ir [Ir-cat.] <b>7.5</b> conv. = 2%, ee = n.d. [Ir-cat.] <b>7.6</b> conv. = 2%, ee = n.d.</p>		

Conversion determined by GC on an achiral stationary phase; Enantiomeric excess determined by HPLC on a chiral stationary phase.

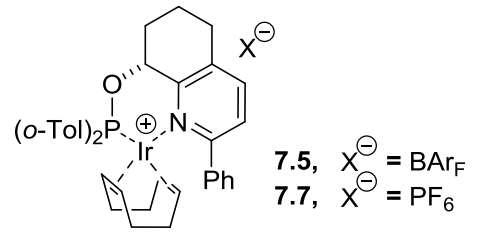
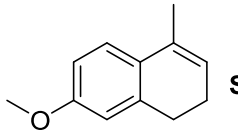
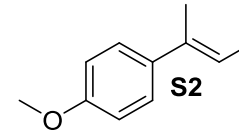
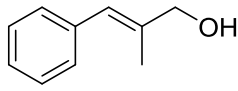
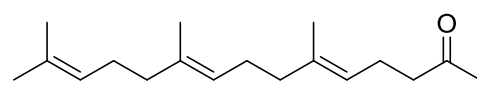
### 7.3 Influence of the counterion for catalyst **7.5**

As already discussed in the case of iridium PHOX catalysts, the counterion has a significant influence on the conversion reached in the hydrogenation of olefins (chapter 1).<sup>[27]</sup> Tetrakis(3,5-bis-trifluoromethyl-phenyl)borate ( $\text{BAr}_\text{F}$ ) emerged as the counterion of choice



showing significantly longer life time of the active catalytic species. Although the application of  $\text{BAr}_\text{F}$  as counterion results in the formation of a more robust catalyst, this anion is not ideal owing to its high price and molecular weight. It was observed that the  $\text{PF}_6$  salt reacts with lower rates compared to  $\text{BAr}_\text{F}$ , although they are still respectable.<sup>[27]</sup> However, these complexes undergo the previously mentioned deactivation to the trinuclear cluster of the type of **7.2**. The formation of such a trinuclear cluster was not observed for the iridium complex **7.5** under hydrogen atmosphere in the absence of substrate. As a consequence we wondered if a counterion exchange might result in the formation of a less expensive catalyst with similar properties. Therefore the  $\text{PF}_6$ -analog of catalyst **7.7** was synthesized and its behavior in the presence and absence of a substrate was investigated. First, the two analogs were compared in the hydrogenation of different model substrates (table 7.2). The data obtained with  $\text{PF}_6$  **7.7** and  $\text{BAr}_\text{F}$ -analog **7.5** revealed that higher conversions are obtained with the latter. For the allyl alcohol **S8** even more than 11 times higher conversion was observed. Only (5*E*,9*E*)-farnesylacetone **7.8** was converted almost completely to the fully saturated substrate regardless of the catalyst used. Also the enantioselectivity remained lower for the iridium complex with the  $\text{PF}_6$  counterion compared to its analog  $\text{BAr}_\text{F}$  salt.

**Table 7.2:** Hydrogenation of selected model substrates by the use of the PF<sub>6</sub> and BAr<sub>F</sub> analogs **7.5** and **7.7**.

$  \begin{array}{c}  \text{R}^1 \quad \text{R}^3 \\  \diagdown \quad \diagup \\  \text{C} \\  \diagup \quad \diagdown \\  \text{R}^2  \end{array}  \xrightarrow[\text{CH}_2\text{Cl}_2 \text{ (0.2 M), RT, 2 h}]{1.0 \text{ mol\% [Ir-cat.], 50 bar H}_2}  \begin{array}{c}  \text{R}^1 \quad \text{R}^3 \\  \diagdown \quad \diagup \\  \text{C}^* \\  \diagup \quad \diagdown \\  \text{R}^2  \end{array}  $			
 <p><b>S5</b></p> <p>[Ir-cat.] <b>7.5</b>: conv. = &gt;99%, ee = 92% (S)  [Ir-cat.] <b>7.7</b>: conv. = 31%, ee = 63% (S)</p>		 <p><b>S2</b></p> <p>[Ir-cat.] <b>7.5</b>: conv. = &gt;99%, ee = 99% (R)  [Ir-cat.] <b>7.7</b>: conv. = 50%, ee = 90% (R)</p>	
 <p><b>S8</b></p> <p>[Ir-cat.] <b>7.5</b>: conv. = &gt;99%, ee = 87% (S)  [Ir-cat.] <b>7.7</b>: conv. = 9%, ee = n. d.</p>		 <p><b>7.8</b></p> <p>[Ir-cat.] <b>7.5</b>: <b>7.8</b> + 6H<sub>2</sub> = &gt;99%, ee = n.d.  [Ir-cat.] <b>7.7</b>: <b>7.8</b> + 6H<sub>2</sub> = 96%, ee = n.d.</p>	

Conversion determined by GC on an achiral stationary phase; Enantiomeric excess determined by HPLC on a chiral stationary phase.

To get a better insight on the different behavior of these two catalysts, the conversion after 2 h and 15.5 h in the hydrogenation of (5*E*,9*E*)-farnesylacetone (**7.8**) was determined at reduced catalyst loading (table 7.3). The hydrogenation conducted with the BAr<sub>F</sub> salt **7.5** showed after 2 h still reactivity and conversion to the fully reduced product **7.9** raised from 35% after 2 h to 82% after 15.5 h. For the PF<sub>6</sub> salt **7.7** the conversion raised only from 19% to 23% comparing the results after 2 h and 15.5 h.

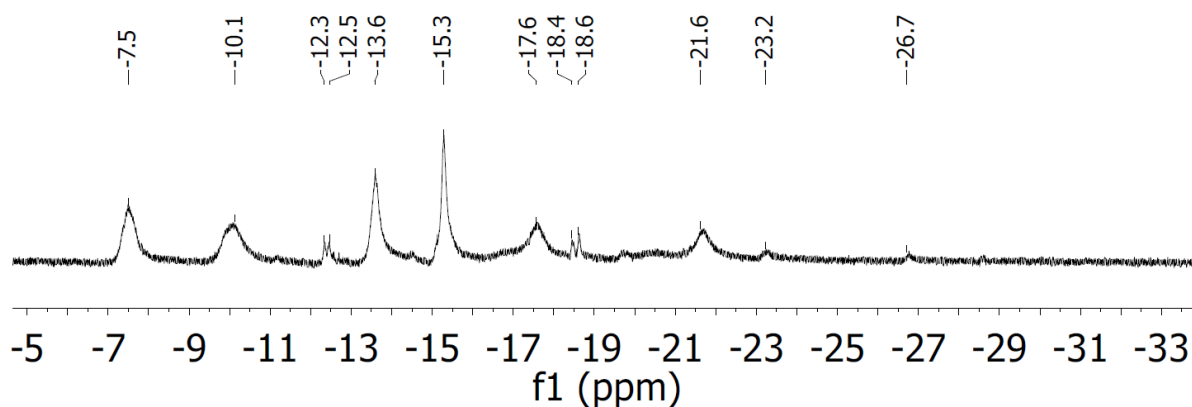
**Table 7.3:** Hydrogenation of (5*E*,9*E*)-farnesylacetone (**7.8**) at reduced catalyst loading.

$  \begin{array}{c}  \text{7.8}  \end{array}  \xrightarrow[\text{CH}_2\text{Cl}_2 \text{ (0.2 M), RT, time}]{0.3 \text{ mol\% [Ir-cat.], 50 bar H}_2}  \begin{array}{c}  \text{7.9}  \end{array}  $			
		<b>7.9</b> [%] <sup>[a]</sup>	
<b>[Ir-cat.]</b>		2 h	15.5 h
<b>7.5</b>		35	82
<b>7.7</b>		19	23

[a] Determined by GC analysis on an achiral stationary phase.

With these results in hand, it became clear that the pyridine-based catalyst **7.5** bearing BAr<sub>F</sub> as counterion is longer active when compared to its PF<sub>6</sub> analog **7.7**. This is in agreement with

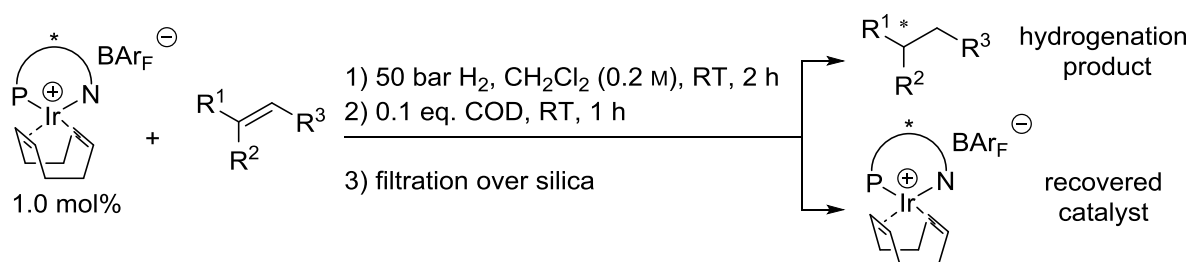
the results obtained in the detailed study conducted by Smidt *et al.* on the counterion influence for PHOX-based iridium catalysts.<sup>[27]</sup> Furthermore, NMR studies of the PF<sub>6</sub>-analog **7.7** in the presence of hydrogen revealed, that the selective formation of the previously described dimeric Ir-hydride complex **7.6** was no longer observed after counterion exchange. The spectra showed a complex mixture of different hydride species (figure 7.1).



**Figure 7.1:** <sup>1</sup>H NMR spectrum of the hydride region collected for catalyst **7.7** after the application of 50 bar H<sub>2</sub>.

## 7.4 Recovery of different catalyst classes from the reaction mixture

With promising results in hand obtained in the study of the  $\text{BAr}_\text{F}$ -analog of catalyst **7.5**, a potential recovery after the hydrogenation of model substrates in combination with different catalysts was tested. Therefore, the following protocol, which represents a slight modification of a typical hydrogenation procedure was applied. First, the substrate was stirred in the presence of 1.0 mol% iridium complex under 50 bar hydrogen atmosphere for 2 h without measuring the conversion. After release of  $\text{H}_2$ , 0.1 eq. of COD was added and the reaction mixture was stirred for 1 h followed by evaporation of the solvent. The residue was separated by a simple filtration over a short plug of silica. First eluting the substrate and the excess of COD with a mixture of pentane: $\text{Et}_2\text{O}$  (4:1), followed by pure  $\text{CH}_2\text{Cl}_2$  afforded recovered iridium complex. The excess of COD was removed in high vacuum.

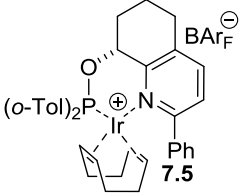
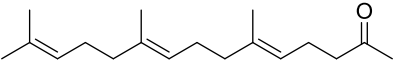
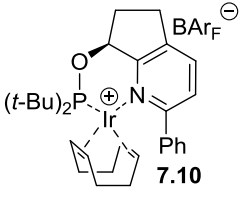
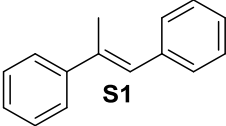
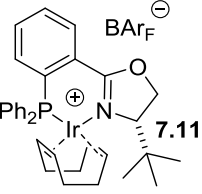
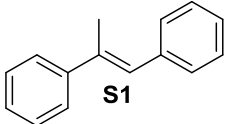
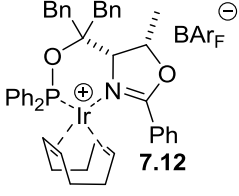
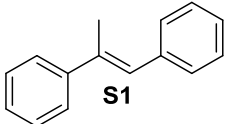


**Scheme 7.5:** Schematic diagram of the protocol applied for the recovery of the catalyst from the reaction mixture.

In this context four different catalysts were investigated: the two most broadly applied pyridine-based catalysts **7.5** and **7.10**, the complex **7.11** of the PHOX family (one of the first applied iridium catalyst in the asymmetric hydrogenation of unfunctionalized double bonds) and commercially available ThrePHOX catalyst **7.12**.

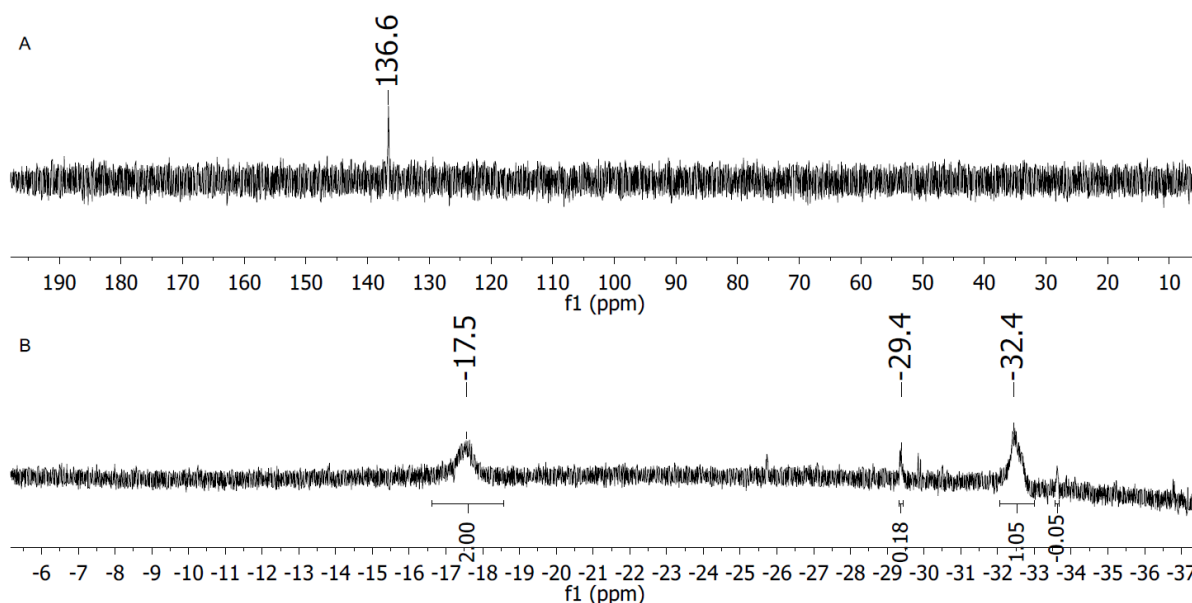
Indeed, the obtained data revealed, that the protocol depicted in scheme 7.5 allows for the recovery of different catalysts after the complete hydrogenation of the substrate. As expected, this method is not viable for all catalysts (table 7.4). However, only for the ThrePHOX catalyst **7.12** this method was not successful. The three other catalysts were recovered in yields between 60 and 70% with this slight modification of a typical hydrogenation procedure.

**Table 7.4:** Recovery of different hydrogenation catalysts from the reaction mixture (conditions see scheme 7.5).

Entry	Cat.	Substrate <sup>[a]</sup>	Amount of cat. [mg]	Recovered cat. [%]
1	 7.5	 7.8	40	70
2	 7.10	 S1	30	60
3	 7.11	 S1	30	67
4	 7.12	 S1	25	0

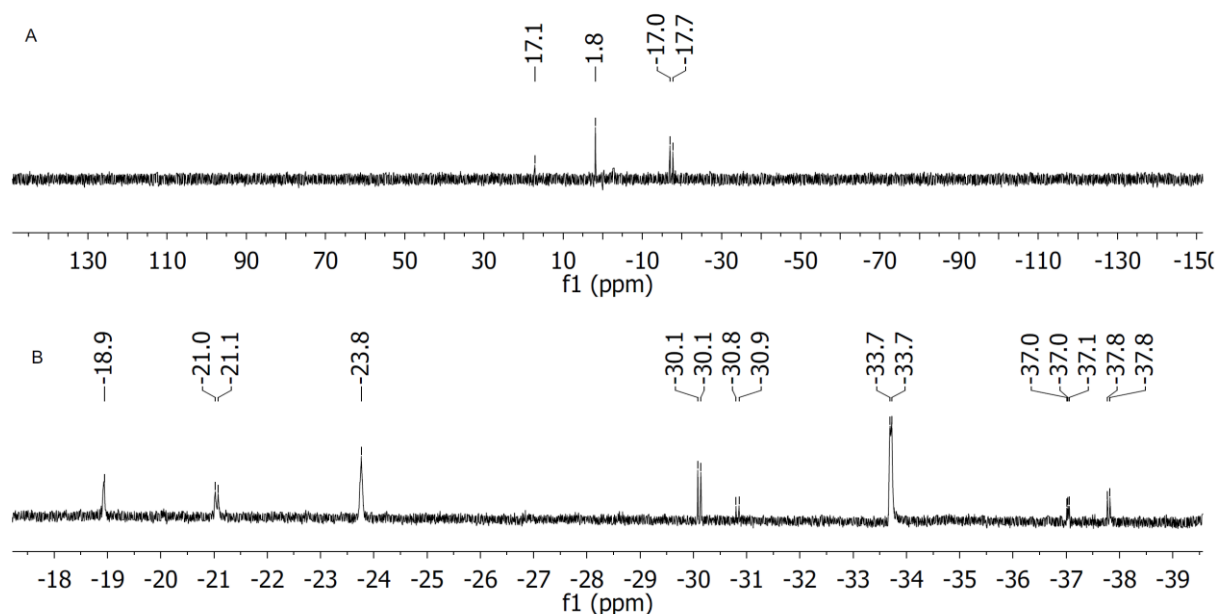
[a] Full conversion was obtained for all entries.

In light of these results, we wondered whether catalysts **7.10** and **7.11** form a similar dimeric species as previously described for catalyst **7.5** under hydrogen atmosphere. The <sup>31</sup>P NMR spectra of complex **7.10** after treatment with 50 bar H<sub>2</sub> for 2 h showed the appearance of one new broad signal at 136.6 ppm (compared to 141.8 ppm for the COD iridium complex) with a width of over 53 Hz (figure 7.2, **A**). The <sup>1</sup>H NMR spectrum showed also broad peaks. Predominantly two broad peaks, with completely different shifts compared to the dimer **7.6**, were observed (figure 7.2, **B**). The broad signals made it difficult at this point to identify the nature of the major species. Low temperature NMR experiments could have helped with the identification of this species but were not conducted up to this point.



**Figure 7.2:**  $^{31}\text{P}$  NMR spectrum of catalyst **7.10** after applying 50 bar  $\text{H}_2$ , **A**; hydride region of catalyst **7.10** after applying 50 bar  $\text{H}_2$ , **B**.

The NMR studies of the PHOX catalyst **7.11** after applying 50 bar hydrogen pressure showed a completely different picture. In this case, several new signals in the  $^{31}\text{P}$  NMR and in the hydride region of the  $^1\text{H}$  NMR appeared (figure 7.3). Such new signals could not be assigned to a major species. This process is interesting especially for catalyst **7.11** since 67% of it could be recovered after the hydrogenation reaction. That it was still possible to recover 67% of the catalyst might be explained by the assumption that the different species are in equilibrium under hydrogen atmosphere. Therefore, one or more of these species could be reconverted to precatalyst **7.11** by the addition of COD. Another explanation could be that the amount of the formed polyclusters species is significantly smaller under normal hydrogenation conditions, which are roughly 10 times more diluted compared to the NMR experiments.

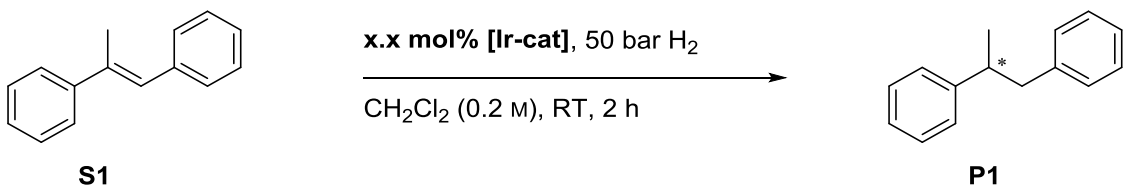


**Figure 7.3:** A:  $^{31}\text{P}$  NMR spectrum of the of catalyst **7.11** after applying 50 bar  $\text{H}_2$ ; B: hydride region of under identical conditions as A.

## 7.5 Hydrogenations with recovered catalyst

To confirm, that the recovered catalyst **7.11re** performs with similar reactivity and selectivity compared to the original catalyst, these two complexes were compared in the hydrogenation of *trans*- $\alpha$ -methylstilbene (**S1**). The obtained data reveal no difference between the original and the recovered catalyst. At 1.0 and 0.2 mol% catalyst loading identical enantiomeric excesses were observed (table 7.5). The reaction with the recovered catalyst **7.11re** showed an even slightly higher conversion. Although this difference in reactivity is within the range of tolerated experimental error, a possible explanation for the observed increased reactivity could be that the quality of the recovered catalyst is somehow higher than that of the older batch of the same complex, that might have undergone oxidation and degradation processes.

**Table 7.5:** Hydrogenation of *trans*- $\alpha$ -methylstilbene (**S1**) with two different batches of catalyst **7.11** and **7.11re**.



Entry <sup>[a]</sup>	[Ir-cat.]	Cat. loading [mol%]	Conv. [%] <sup>[b]</sup>	<i>ee</i> [%] <sup>[c]</sup>
1	<b>7.11</b>	1	>99	86 ( <i>R</i> )
2	<b>7.11re</b>	1	>99	86 ( <i>R</i> )
3	<b>7.11</b>	0.2	37	87 ( <i>R</i> )
4	<b>7.11re</b>	0.2	40	87 ( <i>R</i> )

[a] Reaction run on 0.1 mmol scale; [b] Determined by GC analysis on an achiral stationary phase; [c] Determined by HPLC analysis on a chiral stationary phase.

## 7.6 Conclusion

In summary, in collaboration with Dr. Stefan Gruber, it was successfully demonstrated that it is possible to recover Ir-N,P ligand complexes effectively and easily from the reaction mixture by the addition of COD. By simple filtration over a short plug of silica the recovered catalyst can be separated from the hydrogenation product and recovered in up to 70% yield. The application of such a protocol is particularly interesting for reactions conducted on a larger scale and for catalysts which are difficult to synthesize and therefore more expensive. In addition, this concept might become interesting for reactions that normally require longer reaction times. In this case, a higher catalyst loading could significantly shorten the reaction times and the catalyst could be recovered afterwards from the reaction mixture. It was also shown that the recovery of the iridium complexes is not possible for every catalyst and substrate combination. However, assuming that the decomposition rate of the catalyst increases when the substrate is used up, there might be significant potential for optimizations of this procedure with increasing yields for the catalyst just by monitoring the reaction progress.

This approach has significant advantages over the only previous example reported on the recovery of Ir-N,P ligand complexes by Börner and co-workers.<sup>[127]</sup> In their work, propylene carbonate was utilized as solvent and the substrate was extracted after the reaction by the addition of hexane whereas the catalyst remained in the propylene carbonate layer. The fact that hydrogenation conducted in propylene carbonate show lower conversion and longer



reaction times, and that this method can only be applied to substrates being insoluble in propylene carbonate makes the new procedure for catalyst recovery clearly superior.



## Chapter 8

# Experimental Part

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## 8.1 General Informations

### 8.1.1 Working Techniques

Commercially available reagents were purchased from Acros, Aldrich, Alfa-Aesar, Fluka, Fluorochem, Frontier Scientific, Maybridge, Strem or TCI and used as received without further purification unless otherwise noted. The solvents were collected from a purification column system (PureSolv, Innovative Technology Inc.)<sup>[128]</sup> or purchased from Aldrich or Fluka in sure/sealed<sup>TM</sup> bottles over molecular sieves. Column chromatographic purifications were performed on Fluka silica gel 60 (particle size 40-63 nm) according to the procedure published by *Still* and *Mitra*.<sup>[129]</sup> The eluents were of technical grade and distilled prior to use. As far as not mentioned external temperature data was assigned. If nothing different is noted a high vacuum of 0.05 mbar was applied.

### 8.1.2 Analytical Methods

**Thin Layer Chromatography (TLC):** TLC plates were obtained from Macherey-Nagel (Polygram SIL G/UV254, 0.2 mm silica with fluorescence indicator, 40 × 80 mm). For visualization UV light (254 nm, 366 nm) or basic permanganate solution [KMnO<sub>4</sub> (3.0 g), K<sub>2</sub>CO<sub>3</sub> (20 g), 5% aq. NaOH (5 mL), H<sub>2</sub>O (300 mL)] were used.

**Melting Points (MP):** Melting points were determined on a Büchi B-545 apparatus and were not corrected.

**Nuclear Magnetic Resonance-Spectroscopy (NMR):** NMR spectra were measured either on a Bruker DPX-NMR (400MHz), on a Bruker BZH NMR (250 MHz) or a Bruker Avance DRX-NMR (500 MHz) spectrometer equipped with BBO broadband probe heads. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) relative to residual solvent peaks and coupling constants ( $J$ ) are reported in (Hz). Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). The measurements were performed at 25 °C, if nothing else is reported. The chemical shift  $\delta$  values were corrected to 7.26 ppm (<sup>1</sup>H NMR)<sup>[130]</sup> and 77.16 ppm (<sup>13</sup>C NMR)<sup>[130]</sup> for CHCl<sub>3</sub>, 5.32 ppm (<sup>1</sup>H NMR)<sup>[130]</sup> and 54.0 ppm (<sup>13</sup>C NMR)<sup>[130]</sup> for CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>OH 3.31 (<sup>1</sup>H NMR)<sup>[130]</sup> and 49.0 ppm (<sup>13</sup>C NMR)<sup>[130]</sup>. <sup>31</sup>P NMR spectra were calibrated relative to 85% phosphoric acid ( $\delta$  = 0 ppm), <sup>19</sup>F NMR spectra relative to CFC<sub>3</sub> ( $\delta$  = 0 ppm) and <sup>11</sup>B NMR spectra relative to BF<sub>3</sub>·OEt<sub>2</sub> ( $\delta$  = 0 ppm) as external standards. The assignment of <sup>1</sup>H and <sup>13</sup>C signals was partly made by DEPT and 2D-NMR, namely COSY, HMQC, HMBC and NOSY. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, m = multiplet. The note br indicates a broad signal shape.

**Mass Spectrometry (MS):** Mass spectra were measured by Dr. H. Nadig (Department of Chemistry, University of Basel) on a VG70-250 (electron ionization (EI)) mass spectrometer or a Finnigan MAR 312 (fast atom bombardment (FAB)) mass spectrometer. FAB was performed with 3-nitrobenzyl alcohol (NBA) as matrix. ESI-MS spectra were measured by Dr.

C. Ebner, Mr. F. Bächle or Mr P. Isenegger (Department of Chemistry, University of Basel) on a Finnigan MAT LCQ Varian Quadropol 1200 MS/MS spectrometer. The signals are given in mass to charge ratio ( $m/z$ ) with the relative intensities in brackets.

**Mass Spectrometry (HRMS-EI):** Mass spectra were measured by O. Greter (Mass Spectrometry Service Facility at LOC, ETH Zurich) on a Waters' Micromass AutoSpec Ultima (EI-triSector-MS).

**Mass Spectrometry (HRMS-ESI):** Mass spectra were measured by Dr. H. Nadig (Department of Chemistry, University of Basel) on a Bruker maXis 4G.

**Infrared Spectroscopy (IR):** The IR spectra were recorded on a Shimadzu FTIR-8400S Fourier Transform spectrometer with ATR/Golden Gate technology. Infrared spectra of liquids collected between two sodium chloride plates or those of solid samples in a potassium bromide matrix were measured on a Perkin Elmer 1600 series FTIR spectrometer. The absorption bands are given in wave numbers  $\tilde{\nu}$  ( $\text{cm}^{-1}$ ). The peak intensity is assigned with s (strong), m (medium) and w (weak). The note br stands for a broad peak shape.

**Elemental Analysis (EA):** Elemental analyses were measured by Mr. W. Kirsch or Sylvie Mittelheiser (Department of Chemistry, University of Basel) on a Leco CHN-900 analyzer or on a Vario Micro Cube by Elementar (C-, H-, N detection). The data are indicated in mass percent.

**Optical Rotation ( $[\alpha]_D^{20}$ ):** Optical rotations were measured on a Perkin Elmer Polarimeter 341 in a 1 dm cuvette at 20 °C. The concentration (c) is given in g/100 mL.

**Gas Chromatography (GC):** Gas chromatograms were collected on Shimadzu GC 2010-Plus or Carlo Erba HRGC Mega2 Series 800 (HRGS Mega2) instruments. Achiral separations were performed on a Restek Rtx®-1701 column (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) or on a Optima 5-Amine (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) using He as carrier gas. For the separations of enantiomers *ChiralDEX G-TA*,  $\gamma$ -cyclodextrin TFA column (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ), *Macherey-Nagel* Hydrodex- $\beta$ -3P (25 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ), *Brechbühler SE54*  $\beta$ -cyclodextrin DETBUTSIL (25 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ), *Varian* CP Chirasil-dex CB (25 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ), *Varian* CP-Sil 88 (50 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) were used with  $\text{H}_2$  as carrier gas.

**Gas Chromatography-Mass Spectrometry (GC-MS):** The GC-MS spectra were recorded on a Shimadzu GCMS-QP2010 SE equipped with a Restek Rtx®-5MS column (30 m  $\times$  0.2 mm  $\times$  0.2  $\mu\text{m}$ ). For this instrument the carrier gas was He. In addition a HP5890 gas chromatograph with a HP5970A detector equipped with a Macherey and Nagel Optima5 (5% polyphenylmethylsiloxane column, 25 m  $\times$  0.2 mm  $\times$  35  $\mu\text{m}$ ) and a HP5890 gas chromatograph with a HP5971 detector equipped with a Agilent HP1 (1% dimethylsiloxane column, 15 m  $\times$  0.2 mm  $\times$  33  $\mu\text{m}$ ) were used. For both instruments the flow was set to 1 mL/min with 20:1 split ratio.

**High Performance Liquid Chromatography (HPLC):** HPLC analysis was measured on Shimadzu Class-VP Version 5.0 systems with SCL-10A system controller, LC-10AD pump

system, SIL-10AD auto injector, CTO-10AC column oven, DGU-14A degasser and SPD-M10A diode array- or UV/VIS detector or on Shimadzu LC-20A prominence with LC-20AD pump system, SIL-20AHT auto injector, CTO-10AS column oven, SPD-M20A diode array, DGU-20A3 degasser. Chiral columns *Chiralcel* OD-H, OJ and OJ-H or *Chiralpak* AD-H, IC and AS-H (4.6 mm  $\times$  250 mm) from Daicel Chemical Industries were used.

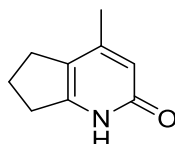
**Semipreparative High Performance Liquid Chromatography (Semipreparative HPLC):**

Separations by semipreparative HPLC were performed on Shimadzu systems with SIL 10 Advp autosampler, CTO 10 ASVP column oven, LC 10 Atvp pump system, FCV 10 Alvp degasser and SPD M10 Acp diode array detector. As column with chiral stationary phase *Chiralcel* OD (2  $\times$  25 cm) from Daicel Chemical Industries was used.

## 8.2 Development and study of pyridyl phosphite based catalyst with sterically demanding aryl substituents

### 8.2.1 Synthesis of chiral pyridyl alcohols

#### 4-Methyl-1,5,6,7-tetrahydro-2H-cyclopenta[b]pyridin-2-one (2.24)



A mixture of ethyl acetoacetate (116 g, 113 mL, 0.89 mol, 1.00 eq.), cyclopentanone (84.0 g, 88.5 mL, 1.00 mol, 1.12 eq.) and ammonium acetate (77.8 g, 1.00 mol, 1.12 eq.) was stirred for 18 h at reflux. The reaction mixture was concentrated to a volume of 90 mL. The residue was filtered off and washed with Et<sub>2</sub>O (50 mL) and H<sub>2</sub>O (50 mL). Recrystallization from H<sub>2</sub>O (3.0 L) followed by recrystallization from ethyl acetate (1.0 L) afforded the product (19.5 g, 0.13 mol, 15%) as a pale gray solid.

C<sub>9</sub>H<sub>11</sub>NO (149.19 g/mol):

**MP:** 248 °C.

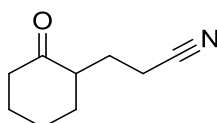
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 13.04 (s, 1H, NH), 6.20 (s, 1H, ar-*H*), 2.90 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H, CH<sub>2</sub>), 2.67 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 2H, CH<sub>2</sub>), 2.13 (s, 3H, CH<sub>3</sub>), 2.17-2.05 (m, 2H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 166.3 (s, C=O), 151.2 (s, ar-*qC*), 148.5 (s, ar-*qC*), 120.8 (s, ar-*qC*), 115.4 (s, ar-*C*), 31.3 (s, CH<sub>2</sub>), 28.6 (s, CH<sub>2</sub>), 22.5 (s, CH<sub>2</sub>), 20.0 (s, CH<sub>3</sub>).

**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 3449 (w), 2858 (m), 1654 (s), 1620 (m), 1578 (m), 1470 (m), 1426 (m), 1371 (w), 1327 (m), 1220 (w), 1176 (w), 1026 (w), 933 (m), 901 (w), 860 (w), 806 (w).

Obtained data are in accordance with literature data.<sup>[57c]</sup>

#### 3-(2-Oxocyclohexyl)propanenitrile (2.22)



A solution of cyclohexanone (64.0 mL, 60.6 g, 618 mmol, 1.00 eq.), acrylonitrile (43.4 mL, 34.8 mL, 648 mmol, 1.05 eq.), cyclohexylamine (2.54 mL 2.21 g, 22.2 mmol, 0.04 eq.) and



acetic acid (248  $\mu$ L, 260 mg, 4.32 mmol, 0.01 eq.) was stirred for 3 h at 120 °C. All volatiles were removed under reduced pressure and the residue was diluted with Et<sub>2</sub>O (300 mL) and washed with 1 M HCl solution (3  $\times$  100 mL). The organic layer was dried over MgSO<sub>4</sub> and the solvent evaporated under reduced pressure. Distillation of the residue (0.6 mbar, 110 °C) afforded the product (67.0 g, 444 mmol, 72%) as a colorless oil.

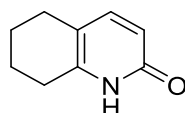
C<sub>9</sub>H<sub>13</sub>NO (151.21 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 2.47-2.22 (m, 5H, alkyl-*H*), 2.13-1.90 (m, 3H, alkyl-*H*), 1.90-1.74 (m, 1H, alkyl-*H*), 1.71-1.24 (m, 4H, alkyl-*H*).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 211.7 (s, C=O), 119.7 (s, C $\equiv$ N), 48.8 (s, CH), 42.1 (s, CH<sub>2</sub>), 34.1 (s, CH<sub>2</sub>), 27.9 (s, CH<sub>2</sub>), 25.6 (s, CH<sub>2</sub>), 25.1 (s, CH<sub>2</sub>), 15.1 (s, CH<sub>2</sub>).

Obtained data are in accordance with literature data.<sup>[131]</sup>

### 5,6,7,8-Tetrahydroquinolin-2(1H)-one (2.25)



3-(2-Oxocyclohexyl)propanenitrile (30.0 g, 198 mmol, 1.00 eq.) was added to 98% sulfuric acid (200 mL) over a period of 45 min at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for additional 45 min. The reaction mixture was poured on a mixture of crushed ice (1 kg) and 32% ammonium hydroxide solution (430 mL). The aqueous solution was extracted with chloroform (3  $\times$  150 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the solvent evaporated under reduced pressure. The residue was recrystallized from H<sub>2</sub>O (800 mL) to afford the product (13.9 g, 93.2 mmol, 47%) as a colorless solid.

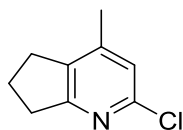
C<sub>9</sub>H<sub>11</sub>NO (149.19 g/mol):

**MP:** 208-210 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 13.29 (s, 1H, NH), 7.15 (d, *J* = 9.1 Hz, 1H, ar-*H*), 6.33 (d, *J* = 9.1 Hz, 1H, ar-*H*), 2.66 (t, *J* = 6.1 Hz, 2H, CH<sub>2</sub>), 2.44 (t, *J* = 5.8 Hz, 2H, CH<sub>2</sub>), 1.92-1.30 (m, 4H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 165.1 (s, C=O), 143.8 (s, ar-C), 143.3 (s, ar-C), 116.8 (s, ar-C), 114.5 (s, ar-C), 26.8 (s, CH<sub>2</sub>), 26.1 (s, CH<sub>2</sub>), 22.6 (s, CH<sub>2</sub>), 21.7 (s, CH<sub>2</sub>).

Obtained data are in accordance with literature data.<sup>[132]</sup>

**2-Chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (2.26)**

A solution of 4-methyl-1,5,6,7-tetrahydro-2H-cyclopenta[b]pyridin-2-one (19.5 g, 130 mmol, 1.00 eq.) in phenylphosphoryl dichloride (49.7 mL, 353 mmol, 2.71 eq.) was stirred for 18 h at reflux under an inert atmosphere. The reaction mixture was poured into an Erlenmeyer flask containing a mixture of H<sub>2</sub>O (250 mL), chloroform (250 mL), sodium carbonate (58 g) and ice (~750 g). The pH-value was adjusted to 8 by addition sodium carbonate. The organic phase was separated and the aqueous phase was separate and extracted with chloroform (3 × 150 mL). The combined organic layers were dried over MgSO<sub>4</sub> and all volatiles evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation (190 °C, 3 mbar) to afford the product (17.5 g, 104 mmol, 80%) as a colorless solid.

C<sub>9</sub>H<sub>10</sub>ClN (167.64 g/mol):

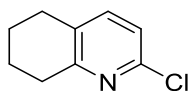
**MP:** 49-54 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 6.91 (s, 1H, ar-*H*), 2.99 (t, <sup>3</sup>*J*<sub>HH</sub> = 5.0 Hz, 2H, CH<sub>2</sub>), 2.83 (t, <sup>3</sup>*J*<sub>HH</sub> = 5.0 Hz, 2H, CH<sub>2</sub>), 2.23 (s, 3H, CH<sub>3</sub>), 2.13 (tt, <sup>3</sup>*J*<sub>HH</sub> = 5.0 Hz, <sup>3</sup>*J*<sub>HH</sub> = 5.0 Hz, 2H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 166.7 (s, ar-*qC*), 149.4 (s, ar-*qC*), 146.1 (s, ar-*qC*), 135.3 (s, ar-*qC*), 122.0 (s, ar-*C*), 34.3 (s, CH<sub>2</sub>), 28.8 (s, CH<sub>2</sub>), 22.6 (s, CH<sub>2</sub>), 19.0 (s, CH<sub>3</sub>).

**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 3448 (w), 2955 (m), 2920 (m), 2840 (w), 1588 (s), 1563 (s), 1429 (s), 1377 (s), 1307 (m), 1264 (m), 1188 (m), 1099 (s), 883 (s).

Obtained data are in accordance with literature data.<sup>[56]</sup>

**2-Chloro-5,6,7,8-tetrahydroquinoline (2.27)**

5,6,7,8-Tetrahydro-2(1H)-quinolinone (4.66 g, 31.2 mmol, 1.00 eq.) was added in a 50 mL two-necked flask. The flask was flushed with argon for 5 min and phenylphosphonic dichloride (11.9 mL, 86.4 mmol, 2.80 eq.) was added. The yellow reaction mixture was stirred for 17 h at 150 °C. The resulting brown oil was poured onto a mixture of K<sub>2</sub>CO<sub>3</sub> and crushed ice (20 g/180 g) and CHCl<sub>3</sub> (40 mL) was added. The suspension was stirred for 1 h at room

temperature. The phases were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 40$  mL). The combined organic layers were dried over  $\text{MgSO}_4$  and filtered. The solvent was evaporated under reduced pressure and the resulting brown oil was purified by bulb-to-bulb distillation ( $130^\circ\text{C}$ ,  $0.17$  mbar) to afford the product ( $4.98$  mg,  $29.8$  mmol,  $96\%$ ) as a colorless liquid.

$\text{C}_9\text{H}_{10}\text{ClN}$  ( $167.64$  g/mol):

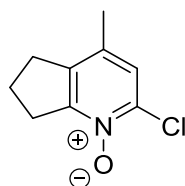
**TLC:**  $R_f = 0.52$  ( $\text{SiO}_2$ , hexane:ethyl acetate (5:1), UV).

**$^1\text{H}$  NMR** ( $400$  MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 7.30$  (d,  $^3J_{\text{HH}} = 7.8$  Hz,  $1\text{H}$ , ar-*H*),  $7.04$  (d,  $^3J_{\text{HH}} = 7.8$  Hz,  $1\text{H}$ , ar-*H*),  $2.88$  (t,  $^3J_{\text{HH}} = 6.4$  Hz,  $2\text{H}$ ,  $\text{CH}_2$ ),  $2.72$  (t,  $^3J_{\text{HH}} = 7.8$  Hz,  $2\text{H}$ ,  $\text{CH}_2$ ),  $1.89$ - $1.83$  (m,  $2\text{H}$ ,  $\text{CH}_2$ ),  $1.81$ - $1.75$  (m,  $2\text{H}$ ,  $\text{CH}_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** ( $101$  MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 158.2$  (s, ar-*C*),  $147.7$  (s, ar-*C*),  $139.7$  (s, ar-*C*),  $131.1$  (s, ar-*C*),  $121.3$  (s, ar-*C*),  $32.3$  (s,  $\text{CH}_2$ ),  $28.1$  (s,  $\text{CH}_2$ ),  $22.7$  (s,  $\text{CH}_2$ ),  $22.5$  (s,  $\text{CH}_2$ ).

Obtained data are in accordance with literature data.<sup>[57b]</sup>

## 2-Chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide (2.28)



*m*CPBA ( $9.15$  g,  $53.0$  mmol,  $1.60$  eq.) was added to a solution of 2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine ( $5.40$  g,  $32.3$  mmol,  $1.00$  eq.) in  $\text{CH}_2\text{Cl}_2$  ( $70$  mL) and the reaction mixture was stirred for  $2$  h at reflux. The obtained yellow solution was washed with sat.  $\text{NaHCO}_3$ -solution ( $3 \times 30$  mL),  $\text{H}_2\text{O}$  ( $3 \times 20$  mL) and brine ( $2 \times 20$  mL). The aqueous layers were back extracted each time with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL). The combined organic layers were dried over  $\text{MgSO}_4$  and filtered. Evaporation of the solvent afforded the product as a colorless solid ( $4.81$  g,  $26.3$  mmol,  $81\%$ ).

$\text{C}_9\text{H}_{10}\text{ClNO}$  ( $183.63$  g/mol):

**MP:**  $79$ - $81^\circ\text{C}$ .

**TLC:**  $R_f = 0.42$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ :MeOH (9:1), UV).

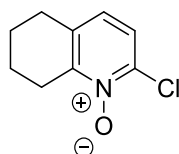
**$^1\text{H}$  NMR** ( $400$  MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 7.14$  (s,  $1\text{H}$ , ar-*H*),  $3.23$  (t,  $^3J_{\text{HH}} = 7.6$  Hz,  $2\text{H}$ ,  $\text{CH}_2$ ),  $2.92$  (t,  $^3J_{\text{HH}} = 7.6$  Hz,  $2\text{H}$ ,  $\text{CH}_2$ ),  $2.22$  (s,  $3\text{H}$ ,  $\text{CH}_3$ ),  $2.22$ - $2.18$  (m,  $2\text{H}$ ,  $\text{CH}_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 153.4 (s, ar-C), 133.8 (s, ar-C), 133.7 (s, ar-C), 125.3 (s, ar-C), 30.7 (s,  $\text{CH}_2$ ), 30.4 (s,  $\text{CH}_2$ ), 22.0 (s,  $\text{CH}_2$ ), 18.0 (s,  $\text{CH}_3$ ).

**IR** (NaCl):  $\tilde{\nu}/\text{cm}^{-1}$  = 3041 (m), 2970 (m), 2928 (m), 2840 (w), 1804 (w), 1606 (w), 1548 (w), 1463 (s), 1440 (s), 1384 (s), 1307 (m), 1272 (s), 1239 (m), 1181 (s), 1076 (m), 1022 (w), 907 (w), 840 (s), 732 (w), 679 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 185.1 (22), 183.1 (68), 169.1 (14), 168.1 (35), 167.1 (48), 166.1 (100), 165.1 (11), 152.1 (17), 151.1 (20), 132.2 (54), 131.1 (96), 130.1 (61), 128.1 (11), 117.1 (17), 103.1 (31), 91.1 (11), 77.1 (29), 65.1 (18), 63.1 (13), 51.1 (20).

### 2-Chloro-5,6,7,8-tetrahydroquinoline 1-oxide (2.29)



*m*CPBA (6.08 g, 35.2 mmol, 1.70 eq.) was added to a solution of 2-chloro-5,6,7,8-tetrahydroquinoline (3.46 g, 20.7 mmol, 1.00 eq.) in  $\text{CH}_2\text{Cl}_2$  (45 mL). The reaction mixture was stirred for 2 h at reflux. The obtained yellow solution was washed with sat.  $\text{NaHCO}_3$ -solution ( $3 \times 30$  mL),  $\text{H}_2\text{O}$  ( $3 \times 20$  mL) and brine ( $2 \times 20$  mL). The aqueous layers were back extracted each time with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL). The combined organic layers were dried over  $\text{MgSO}_4$ . Filtration and evaporation of the solvent afforded the product (3.08 g, 16.7 mmol, 81%) as a brownish solid.

$\text{C}_9\text{H}_{10}\text{ClNO}$  (183.63 g/mol):

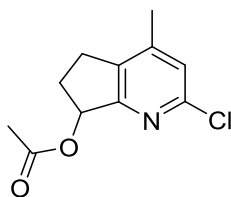
**MP:** 90-94 °C.

**TLC:**  $R_f$  = 0.42 ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ :MeOH (9:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.26 (d,  $^3J_{\text{HH}}$  = 8.0 Hz, 1H, ar-*H*), 6.96 (d,  $^3J_{\text{HH}}$  = 8.0 Hz, 1H, ar-*H*), 2.95 (t,  $J_{\text{HH}}$  = 5.7 Hz, 2H,  $\text{CH}_2$ ), 2.72 (t,  $J_{\text{HH}}$  = 5.7 Hz, 2H,  $\text{CH}_2$ ), 1.88-1.83 (m, 2H,  $\text{CH}_2$ ), 1.76-1.69 (m, 2H,  $\text{CH}_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 150.5 (s, ar-C), 139.1 (s, ar-C), 134.2 (s, ar-C), 125.8 (s, ar-C), 122.9 (s, ar-C), 28.3 (s,  $\text{CH}_2$ ), 25.5 (s,  $\text{CH}_2$ ), 21.7 (s,  $\text{CH}_2$ ), 21.4 (s,  $\text{CH}_2$ ).

Obtained data are in accordance with literature data.<sup>[57b]</sup>

**2-Chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate (2.30)**

A mixture of 2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide (4.12 g, 22.5 mmol, 1.00 eq.) in acetic anhydride (36.0 mL, 39.1 mmol, 9.20 eq.) was stirred at room temperature until all starting material was dissolved (~1 h). Afterwards, the reaction mixture was stirred for 5 h at 80 °C. All volatiles were evaporated under reduced pressure. Column chromatography (SiO<sub>2</sub>, d × h: 3 × 30 cm, hexane → hexane:ethyl acetate (1:2)) afforded the product (2.78 g, 12.3 mmol, 55%) as a colorless oil.

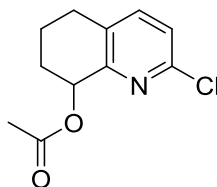
C<sub>11</sub>H<sub>12</sub>ClNO<sub>2</sub> (225.67 g/mol):

**TLC:** R<sub>f</sub> = 0.24 (SiO<sub>2</sub>, hexane:ethyl acetate (5:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.07 (s, 1H, ar-*H*), 6.01 (dd, *J*<sub>HH</sub> = 4.4 Hz, *J*<sub>HH</sub> = 4.4 Hz, 1H, *H*COAc), 3.00-2.91 (m, 1H, CH<sub>2</sub>), 2.80-2.73 (m, 1H, CH<sub>2</sub>), 2.68-2.62 (m, 1H, CH<sub>2</sub>), 2.28 (s, 3H, CH<sub>3</sub>), 2.09 (s, 3H, CH<sub>3</sub>), 2.10-2.02 (m, 1H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 170.8 (s, O<sub>2</sub>CCH<sub>3</sub>), 160.1 (s, ar-C), 150.8 (s, ar-C), 147.3 (s, ar-C), 136.3 (s, ar-C), 124.6 (s, ar-C), 77.2 (s, COAc), 30.6 (s, CH<sub>2</sub>), 26.2 (s, CH<sub>2</sub>), 21.4 (s, O<sub>2</sub>CCH<sub>3</sub>), 18.7 (s, CH<sub>3</sub>).

Obtained data are in accordance with literature data.<sup>[56]</sup>

**2-Chloro-5,6,7,8-tetrahydroquinolin-8-yl acetate (2.31)**

A mixture of 2-chloro-5,6,7,8-tetrahydroquinoline 1-oxide (3.70 g, 20.2 mmol, 1.00 eq.) in acetic anhydride (32.0 mL, 34.3 mmol, 9.20 eq.) was stirred at room temperature until all starting material was dissolved (~1 h). Afterwards, the reaction mixture was stirred for 5 h at 80 °C. All volatiles of the resulting brown solution were evaporated under reduced pressure. Column chromatography (SiO<sub>2</sub>, d × h: 3 × 30 cm, hexane → hexane:ethyl acetate (1:2)) afforded the product (2.07 g, 9.17 mmol, 45%) as a colorless oil.

$C_{11}H_{12}ClNO_2$  (225.67 g/mol):

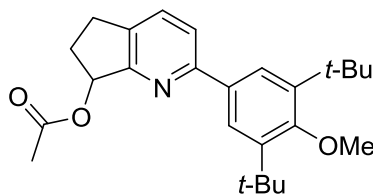
**TLC:**  $R_f = 0.16$  ( $SiO_2$ , hexane:ethyl acetate (10:1), UV).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta/ppm = 7.40$  (d,  $^3J_{HH} = 8.0$  Hz, 1H, ar-*H*), 7.18 (d,  $^3J_{HH} = 8.0$  Hz, 1H, ar-*H*), 5.85 (t,  $J_{HH} = 4.4$  Hz, 1H, *CHOAc*), 2.83 (dt,  $J_{HH} = 16.7, 4.9$  Hz, 1H, *CH*<sub>2</sub>), 2.75-2.67 (m, 1H, *CH*<sub>2</sub>), 2.19-2.12 (m, 1H, *CH*<sub>2</sub>), 2.09 (s, 3H, *CH*<sub>3</sub>), 2.03-1.78 (m, 3H, *CH*<sub>2</sub>).

**$^{13}C\{^1H\}$  NMR** (126 MHz,  $CDCl_3$ ):  $\delta/ppm = 170.3$  (s,  $O_2CCH_3$ ), 153.9 (s, ar-*C*), 149.0 (s, ar-*C*), 140.1 (s, ar-*C*), 132.6 (s, ar-*C*), 124.0 (s, ar-*C*), 70.6 (s, *COAc*), 28.7 (s, *CH*<sub>2</sub>), 27.9 (s, *CH*<sub>2</sub>), 21.5 (s, *CH*<sub>3</sub>), 18.2 (s, *CH*<sub>2</sub>).

Obtained data are in accordance with literature data.<sup>[57b]</sup>

### 2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate



A mixture of 2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide<sup>[133]</sup> (1.73 g, 4.91 mmol, 1.00 eq.) in acetic anhydride (4.61 g, 4.27 mL, 45.2 mmol, 9.20 eq.) was stirred at room temperature until all starting material was dissolved (~1 h). Afterwards, the reaction mixture was stirred for 5 h at 80 °C. All volatiles of the resulting brown solution were evaporated under reduced pressure. Column chromatography ( $SiO_2$ , d × h: 6 × 25 cm, hexane:ethyl acetate (1:4)) afforded the product (1.33 g, 3.34 mmol, 68%) as a colorless solid.

$C_{25}H_{33}NO_3$  (395.54 g/mol):

**MP:** 92-93 °C.

**TLC:**  $R_f = 0.28$  ( $SiO_2$ , hexane:ethyl acetate (5:1), UV).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta/ppm = 7.82$  (s, 2H, ar-*H*), 7.62 (d,  $J_{HH} = 8.0$  Hz, 1H, ar-*H*), 7.55 (d,  $J_{HH} = 8.0$  Hz, 1H, ar-*H*), 6.19 (dd,  $J = 7.3$  Hz,  $J = 4.6$  Hz, 1H, *HCOAc*), 3.72 (s, 3H, *OCH*<sub>3</sub>), 3.09 (ddd,  $J_{HH} = 16.2, 8.7, 5.7$  Hz, 1H, *CH*<sub>2</sub>), 2.90 (ddd,  $J_{HH} = 16.3, 8.4, 5.7$  Hz, 1H, *CH*<sub>2</sub>), 2.64 (dddd,  $J_{HH} = 12.8, 8.5, 7.4, 5.4$  Hz, 1H, *CH*<sub>2</sub>), 2.35 (s, 3H, *CH*<sub>3</sub>), 2.16-2.08 (m, 1H, *CH*<sub>2</sub>), 2.14 (s, 3H, *OCOCH*<sub>3</sub>), 1.48 (s, 18H, 2 × *C(CH*<sub>3</sub>)<sub>3</sub>).

**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta/ppm = 171.2$  (s, *CO*<sub>2</sub>*CH*<sub>3</sub>), 160.8 (s, ar-*C*), 160.7 (s, ar-*C*), 158.3 (s, ar-*C*), 144.1 (s, ar-*C*), 135.3 (s, ar-*C*), 134.1 (s, ar-*C*), 133.6 (s, ar-*C*), 125.9 (s,

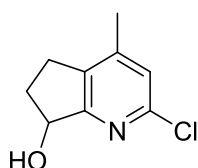
ar-C), 120.8 (s, ar-C), 77.6 (s, COAc), 64.6 (s, OCH<sub>3</sub>), 36.1 (s, C(CH<sub>3</sub>)<sub>3</sub>), 32.3 (s, C(CH<sub>3</sub>)<sub>3</sub>), 31.3 (s, CH<sub>2</sub>), 27.8 (s, CH<sub>2</sub>), 21.6 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3011 (w), 2951 (m), 2907 (w), 2864 (w), 1738 (s), 1591 (m), 1562 (w), 1445 (m), 1410 (m), 1367 (m), 1227 (s), 1161 (s), 970 (m), 891 (m), 827 (s), 781 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 396.3 (13), 395.3 (50), 352.3 (17), 336.3 (14), 335.5 (40), 321.3 (24), 320.2 (100), 290.2 (24), 278.2 (11), 264.2 (10).

**EA** (C<sub>25</sub>H<sub>33</sub>NO<sub>3</sub>): calc.: C 75.91, H 8.41, N 3.54; found: C 76.09, H 8.52, N 3.59.

### 2-Chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (2.32)



K<sub>2</sub>CO<sub>3</sub> (1.52 g, 11.1 mmol, 1.00 eq.) was added to solution of 2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate (2.50 g, 11.1 mmol, 1.00 eq.) in MeOH (40 mL). The yellowish suspension was stirred for 2 h at room temperature. K<sub>2</sub>CO<sub>3</sub> was filtered off and all volatiles were evaporated under reduced pressure. The yellow residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with H<sub>2</sub>O (3 × 30 mL). The organic layer was dried over MgSO<sub>4</sub> and filtered. Evaporation of the solvent afforded the product (1.95 g, 10.7 mmol, 96%) as a colorless oil.

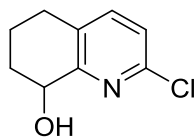
C<sub>9</sub>H<sub>10</sub>ClNO (183.63 g/mol):

**TLC**: R<sub>f</sub> = 0.06 (SiO<sub>2</sub>, hexane:ethyl acetate (5:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta/\text{ppm}$  = 7.02 (s, 1H, ar-H), 5.18 (t,  $J_{\text{HH}}$  = 6.0 Hz, 1H, CHOH), 3.36 (s, 1H, OH), 2.90 (ddd,  $J_{\text{HH}}$  = 16.2 Hz,  $J_{\text{HH}}$  = 9.0 Hz,  $J_{\text{HH}}$  = 4.2 Hz, 1H, CH<sub>2</sub>), 2.68-2.60 (m, 1H, CH<sub>2</sub>), 2.53-2.45 (m, 1H, CH<sub>2</sub>), 2.26 (s, 3H, CH<sub>3</sub>), 2.08-1.99 (m, 1H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta/\text{ppm}$  = 164.7 (s, ar-C), 150.0 (s, ar-C), 147.4 (s, ar-C), 134.8 (s, ar-C), 123.6 (s, ar-C), 74.2 (s, COH), 32.3 (s, CH<sub>2</sub>), 25.6 (s, CH<sub>2</sub>), 18.6 (s, CH<sub>3</sub>).

Obtained data are in accordance with literature data.<sup>[56]</sup>

**2-Chloro-5,6,7,8-tetrahydroquinolin-8-ol (2.33)**

$\text{K}_2\text{CO}_3$  (1.16 g, 8.46 mmol, 1.00 eq.) was added to a solution of 2-chloro-5,6,7,8-tetrahydroquinolin-8-yl acetate (1.91 g, 8.46 mmol, 1.00 eq.) in MeOH (38 mL). The yellowish suspension was stirred for 2 h at room temperature.  $\text{K}_2\text{CO}_3$  was filtered off and all volatiles were evaporated under reduced pressure. The yellow residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (50 mL) and washed with  $\text{H}_2\text{O}$  ( $3 \times 30$  mL). The organic layer was dried over  $\text{MgSO}_4$  and filtered. Evaporation of the solvent afforded the product (1.40 g, 7.62 mmol, 90%) as a colorless oil.

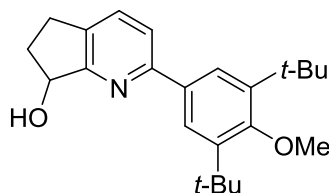
$\text{C}_9\text{H}_{10}\text{ClNO}$  (183.63 g/mol):

**TLC:**  $R_f$  = 0.07 ( $\text{SiO}_2$ , hexane:ethyl acetate (5:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.37 (d,  $J_{\text{HH}}$  = 8.0 Hz, ar-*H*), 7.13 (d,  $J_{\text{HH}}$  = 8.0 Hz, ar-*H*), 4.68 (dd,  $J_{\text{HH}}$  = 6.0 Hz,  $J_{\text{HH}}$  = 5.2 Hz, 1H, *CHOH*), 3.54 (s br, 1H, *OH*), 2.83-2.70 (m, 2H,  $\text{CH}_2$ ), 2.26-2.21 (m, 1H,  $\text{CH}_2$ ), 2.02-1.95 (m, 1H,  $\text{CH}_2$ ), 1.86-1.77 (m, 2H,  $\text{CH}_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 158.8 (s, ar-*C*), 148.5 (s, ar-*C*), 134.0 (s, ar-*C*), 130.7 (s, ar-*C*), 123.1 (s, ar-*C*), 68.7 (s, *COH*), 30.4 (s,  $\text{CH}_2$ ), 27.9 (s,  $\text{CH}_2$ ), 19.3 (s,  $\text{CH}_2$ ).

Obtained data are in accordance with literature data.<sup>[57b]</sup>

**2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol**

A solution of 2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate (1.20 g, 3.03 mmol, 1.00 eq.) in a mixture of MeOH (5 mL), 2 N NaOH solution (2 mL) and THF (5 mL) was stirred for 10 h at room temperature. MeOH and THF were evaporated under reduced pressure. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$ . Column chromatography



(SiO<sub>2</sub>, d × h: 4.5 × 20 cm, cyclohexane:ethyl acetate (1:5)) afforded the the product (1.00 g, 2.83 mmol, 93%) as a colorless solid.

C<sub>23</sub>H<sub>31</sub>NO<sub>2</sub> (353.51 g/mol):

**MP:** 95-97 °C.

**TLC:** R<sub>f</sub> = 0.16 (SiO<sub>2</sub>, hexane:ethyl acetate (5:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.80 (s, 2H, ar-*H*), 7.59 (d, *J*<sub>HH</sub> = 8.0 Hz, 1H, ar-*H*), 7.59 (d, *J*<sub>HH</sub> = 8.0 Hz, 1H, ar-*H*), 5.25-5.22 (m, 1H, *CHOH*), 3.72 (s, 3H, OCH<sub>3</sub>), 3.58 (br s, 1H, OH), 3.01 (ddd, *J*<sub>HH</sub> = 16.1 Hz, *J*<sub>HH</sub> = 8.9 Hz, *J*<sub>HH</sub> = 3.9 Hz, 1H, CH<sub>2</sub>), 2.86-2.78 (m, 1H, CH<sub>2</sub>), 2.59-2.50 (m, 1H, CH<sub>2</sub>), 2.09-2.00 (m, 1H, CH<sub>2</sub>), 1.48 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (100.6 MHz, CDCl<sub>3</sub>): δ/ppm = 164.9 (s, ar-C), 160.9 (s, ar-C), 157.9 (s, ar-C), 144.3 (s, ar-C), 134.3 (s, ar-C), 134.3 (s, ar-C), 133.9 (s, ar-C), 126.0 (s, ar-C), 120.5 (s, ar-C), 75.2 (s, COH), 64.7 (s, OCH<sub>3</sub>), 36.3 (s, C(CH<sub>3</sub>)<sub>3</sub>), 33.41 (s, CH<sub>2</sub>), 32.5 (s, CH<sub>3</sub>), 27.6 (s, CH<sub>2</sub>).

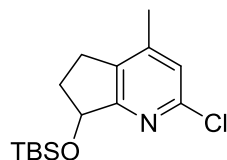
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3412 (w, br), 2959 (m), 2916 (m), 2869 (w), 1466 (m), 1446 (m), 1408 (s), 1360 (m), 1259 (m), 1219 (s), 1113 (m), 1009 (s), 887 (m), 827 (s), 669 (m).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 354.3 (26), 353.3 (100), 339.3 (19), 338.2 (76), 320.2 (14), 290.2 (34), 264.2 (11).

**HRMS** (ESI, 4500 V, 180 °C): (*m/z*) calc. for C<sub>23</sub>H<sub>32</sub>NO<sup>+</sup>: 354.2428 [M+H]<sup>+</sup>; found: 354.2432.

**HPLC:** Daicel, Chiralpak AD-H (0.46 cm × 25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min, 25 °C, 220 nm): t<sub>R</sub> = 10.6 min and 12.2 min.

### 7-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (2.32)



A round bottom flask was charged with 2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (1.39 g, 7.57 mmol, 1.00 eq.), imidazole (1.56 g, 22.7 mmol, 3.00 eq.) and TBSCl (1.71 mg, 11.4 mmol, 1.50 eq.), and purged for 5 min with argon. DMF (12 mL) was added and the resulting colorless solution was stirred for 18 h at room temperature. DMF was evaporated in HV and CH<sub>2</sub>Cl<sub>2</sub> (90 mL) was added. The solution was

washed with H<sub>2</sub>O (3 × 90 mL) and the organic layer was dried over MgSO<sub>4</sub>. Filtration and evaporation of the solvent afforded the product (2.20 g, 7.38 mmol, 98%) as a colorless solid.

C<sub>15</sub>H<sub>24</sub>ClNOSi (297.90 g/mol):

**MP:** 116–117 °C.

**TLC:** R<sub>f</sub> = 0.72 (SiO<sub>2</sub>, hexane:ethyl acetate (5:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 6.97 (s, 1H, ar-*H*), 5.11 (dd, *J*<sub>HH</sub> = 7.0 Hz, *J*<sub>HH</sub> = 4.6 Hz, 1H, CHOSi), 2.92 (ddd, *J*<sub>HH</sub> = 16.1 Hz, *J*<sub>HH</sub> = 8.7 Hz, *J*<sub>HH</sub> = 5.3 Hz, 1H, CH<sub>2</sub>), 2.64 (ddd, *J*<sub>HH</sub> = 14.5 Hz, *J*<sub>HH</sub> = 8.5 Hz, *J*<sub>HH</sub> = 5.5 Hz, 1H, CH<sub>2</sub>), 2.40 (dddd, *J*<sub>HH</sub> = 12.5 Hz, *J*<sub>HH</sub> = 8.5 Hz, *J*<sub>HH</sub> = 7.2 Hz, *J*<sub>HH</sub> = 5.3 Hz, 1H, CH<sub>2</sub>), 2.23 (s, 3H, CH<sub>3</sub>), 2.05–1.97 (m, 1H, CH<sub>2</sub>), 0.91 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 0.20 and 0.15 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>).

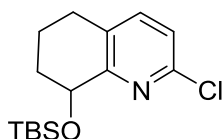
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 164.6 (s, ar-*C*), 150.3 (s, ar-*C*), 146.6 (s, ar-*C*), 134.6 (s, ar-*C*), 123.5 (s, ar-*C*), 75.9 (s, COSi), 33.9 (s, CH<sub>2</sub>), 26.0 (s, C(CH<sub>3</sub>)<sub>3</sub>), 25.7 (s, CH<sub>2</sub>), 18.6 (s, CH<sub>3</sub>), –4.0 and –4.6 (s, Si(CH<sub>3</sub>)<sub>2</sub>).

**IR** (NaCl):  $\tilde{\nu}/\text{cm}^{-1}$  = 2953 (s), 2928 (s), 2855 (s), 1590 (m), 1472 (m), 1441 (s), 1387 (w), 1254 (s), 1189 (m), 1123 (m), 1104 (s), 938 (w), 837 (s), 778 (s).

**MS** (FAB NBA): *m/z* (%): 300.1 (14), 299.2 (12), 298.1 (52), 296.1 (12), 282.1 (17), 242.1 (28), 241.1 (20), 240.1 (100), 168.1 (20), 166.0 (61), 130.0 (10), 75 (21), 73.0 (32).

**EA** (C<sub>15</sub>H<sub>24</sub>ClNOSi): calc.: C 60.48, H 8.12, N 4.70; found: C 60.62, H 8.39, N 4.59.

### 8-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-5,6,7,8-tetrahydroquinoline (2.33)



A round bottom flask was charged with 2-chloro-5,6,7,8-tetrahydroquinolin-8-ol (1.48 g, 8.05 mmol, 1.00 eq.), imidazole (1.66 g, 24.1 mmol, 3.00 eq.) and TBSCl (1.70 g, 11.3 mmol, 1.40 eq.), sealed with a rubber septum and purged for 5 min with argon. DMF (8 mL) was added and the resulting colorless solution was stirred for 18 h at room temperature. DMF was evaporated in HV and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added. The solution was washed with H<sub>2</sub>O (3 × 30 mL) and the organic layer dried over MgSO<sub>4</sub>. Evaporation of the solvent afforded the product (2.06 mg, 6.92 mmol, 86%) as a pale brownish oil.

C<sub>15</sub>H<sub>24</sub>ClNOSi (297.90 g/mol):

**TLC:** R<sub>f</sub> = 0.68 (SiO<sub>2</sub>, hexane:ethyl acetate (5:1), UV).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.32 (d,  $J_{\text{HH}}$  = 8.1 Hz, 1H, ar-*H*), 7.09 (d,  $J_{\text{HH}}$  = 8.1 Hz, 1H, ar-*H*), 4.74 (t,  $J_{\text{HH}}$  = 4.4 Hz, 1H, SiOCH), 2.78 (dt,  $J_{\text{HH}}$  = 17.0 Hz,  $J_{\text{HH}}$  = 5.1 Hz, 1H,  $\text{CH}_2$ ), 2.68-2.61 (m, 1H,  $\text{CH}_2$ ), 2.09-1.96 (m, 2H,  $\text{CH}_2$ ), 1.91-1.85 (m, 1H,  $\text{CH}_2$ ), 1.76-1.70 (m, 1H,  $\text{CH}_2$ ), 0.89 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 0.21 and 0.10 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (126 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 158.2 (s, ar-C), 148.3 (s, ar-C), 139.8 (s, ar-C), 131.1 (s, ar-C), 122.9 (s, ar-C), 69.6 (s, COSi), 32.3 (s,  $\text{CH}_2$ ), 28.0 (s,  $\text{CH}_2$ ), 26.0 (s,  $\text{C}(\text{CH}_3)_3$ ), 18.5 (s,  $\text{C}(\text{CH}_3)_3$ ), 17.9 (s,  $\text{CH}_2$ ), -4.0 and -4.8 (s,  $\text{Si}(\text{CH}_3)_2$ ).

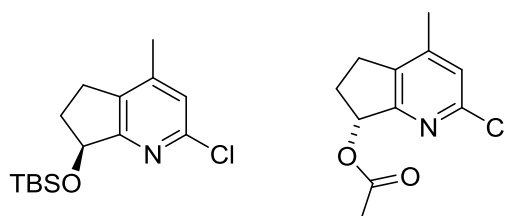
**IR** (NaCl):  $\tilde{\nu}/\text{cm}^{-1}$  = 2950 (s), 2929 (s), 2855 (s), 1580 (m), 1472 (m), 1443 (s), 1360 (w), 1253 (m), 1135 (m), 1089 (s), 991 (s), 881 (m), 835 (s), 778 (s).

**MS** (EI, 70 eV, 25 °C)  $m/z$  (%): 240.1 (100)  $[\text{M}-\text{C}(\text{CH}_3)_3]^+$ , 75.0 (11).

**MS** (FAB NBA):  $m/z$  (%): 300.1 (13), 298.1 (35), 282.1 (14), 242.1 (37), 241.1 (19), 240.1 (100), 168.0 (11), 166.0 (34), 73.0 (26).

**EA** ( $\text{C}_{15}\text{H}_{24}\text{ClNOSi}$ ): calc.: C 60.48, H 8.12, N 4.70; found: C 60.46, H 8.34, N 4.60.

**(*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine ((*S*)-2.36) and (*R*)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridin-7-yl acetate ((*R*)-2.34)**



Vinyl acetate (40.0 mL, 433 mmol, 39.7 eq.) and CAL-B [200 mg, immobilized on acrylic resin from Sigma (L47777)] was added to a solution of 2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridin-7-ol (2.00 g, 10.9 mmol, 1.00 eq.) in dry *i*-Pr<sub>2</sub>O (400 mL). The resulting solution was stirred at 60 °C until HPLC on chiral stationary phase showed full consumption of the (*R*)-enantiomer (20 h). The enzyme was filtered off and washed with EtOAc (3 × 20 mL). Evaporation of the solvent afforded a pale yellow residue which was dissolved in DMF (9 mL). Imidazole (2.22 g, 32.7 mmol, 3.00 eq.) and TBSCl (4.10 g, 27.2 mmol, 2.50 eq.) were added under an argon atmosphere. The resulting colorless solution was stirred for 18 h at room temperature. The solvent was evaporated in HV and the resulting pale yellow residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) and  $\text{H}_2\text{O}$  (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 10 mL). The combined

organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent evaporated under reduced pressure to afford a colorless residue. Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $2 \times 12$  cm, hexane:ethyl acetate ((1:20)  $\rightarrow$  (1:1)) afforded the TBS ether (1.46 g, 4.91 mmol, 40%, >99.9% *ee*) as a colorless solid and the acetate (1.13 g, 5.00 mmol, 41%, 94% *ee*) as a colorless oil.

**HPLC:** *Daicel*, Chiralpak AD-H ( $0.46 \text{ cm} \times 25 \text{ cm}$ , heptane/iso-propanol = 95:05, 0.5 mL/min, 40 °C, 220 nm):  $t_R$  = 12.7 min ((*R*)-acetate (**2.34**), 13.7 min ((*S*)-acetate (**2.34**) and 17.2 min ((*S*)-alcohol **2.32**), 19.5 min ((*R*)-alcohol **2.32**). and

$\text{C}_{15}\text{H}_{24}\text{ClNOSi}$  (297.90 g/mol):

$[\alpha]_D^{20} = +3.9$  ( $c = 0.45$ ,  $\text{CHCl}_3$ ).

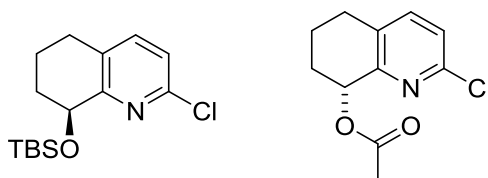
Additional analytical data matches the data of the racemic silyl ether **2.36**.

$\text{C}_{10}\text{H}_{10}\text{ClNO}_2$  (211.65 g/mol):

$[\alpha]_D^{20} = -42.9$  ( $c = 0.88$ ,  $\text{CHCl}_3$ ).

Additional analytical data matches the data of the racemic acetate **2.34**.

**(*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-5,6,7,8-tetrahydroquinoline ((*S*)-**2.37**) and (*R*)-2-chloro-5,6,7,8-tetrahydroquinolin-8-yl acetate ((*R*)-**2.35**)**



Vinyl acetate (120 mL, 1.30 mol, 38.4 eq.) and CAL-B [971 mg, immobilized on acrylic resin from Sigma (L47777)] was added to a solution of 2-chloro-5,6,7,8-tetrahydroquinolin-8-ol (6.20 g, 33.8 mmol, 1.00 eq.) in dry *i*-Pr<sub>2</sub>O (650 mL). The resulting solution was stirred at 60 °C until HPLC on a chiral stationary phase showed full consumption of the (*R*)-enantiomer (20 h). The enzyme was filtered off and washed with EtOAc ( $3 \times 20$  mL). Evaporation of the solvent afforded a pale yellow residue which was dissolved in DMF (35 mL). Imidazole (6.95 g, 102 mmol, 3.00 eq.) and TBSCl (13.1 g, 86.9 mmol, 2.57 eq.) were added under an argon atmosphere. The resulting colorless solution was stirred for 18 h at room temperature. The solvent was evaporated in HV and the resulting pale yellow residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) and  $\text{H}_2\text{O}$  (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  mL). The combined organic layers were

dried over  $\text{MgSO}_4$ , filtered and the solvent evaporated under reduced pressure to afford a colorless residue. Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 15$  cm, hexane:ethyl acetate (1:20  $\rightarrow$  1:1)) afforded the TBS ether (4.60 g, 15.4 mmol, 46%, >99.9% *ee*) as a colorless liquid and the acetate (3.65 g, 16.2 mmol, 48%, 82% *ee*) as a colorless oil.

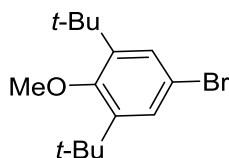
**HPLC:** *Daicel*, Chiralpak AD-H ( $0.46 \text{ cm} \times 25 \text{ cm}$ , heptane/iso-propanol = 95:05, 0.5 mL/min, 40 °C, 220 nm):  $t_R$  = 12.1 min ((*R*)-acetate (**2.35**), 13.8 min ((*S*)-acetate (**2.35**) and 15.8 min ((*S*)-alcohol **2.33**), 17.2 min ((*R*)-alcohol **2.33**).

$\text{C}_{15}\text{H}_{24}\text{ClNOSi}$  (297.90 g/mol):

$[\alpha]_D^{20} = +6.2$  ( $c = 0.68$ ,  $\text{CHCl}_3$ ).

Additional analytical data matches the data of the racemic silyl ether **2.37**.

### 5-Bromo-1,3-di-*tert*-butyl-2-methoxybenzene



4-Bromo-2,6-di-*tert*-butylphenol (5.90 g, 20.7 mmol, 1.00 eq.) was dissolved in DMF (20 mL) and cooled to 0 °C. NaH (60% in mineral oil, 1.83 g, 45.8 mmol, 2.20 eq.) was added in small portions over a period of 20 min. The yellow suspension was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C and MeI (5.07 mL, 82.0 mmol, 4.00 eq.) was added dropwise over a period of 15 min. The resulting red solution was allowed to warm slowly to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and  $\text{H}_2\text{O}$  (50 mL) was added slowly. Hexane (50 mL) was added to the solution and the layers were separated. The aqueous layer was extracted with hexane ( $3 \times 30$  mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated under reduced pressure to obtain a red oil. Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $6 \times 24$  cm, hexane  $\rightarrow$  hexane:ethyl acetate (10:1)) afforded a colorless oil. Drying in HV afforded the product (5.01 g, 16.7 mmol, 81%) as a colorless crystals.

$\text{C}_{15}\text{H}_{23}\text{BrO}$  (299.25 g/mol):

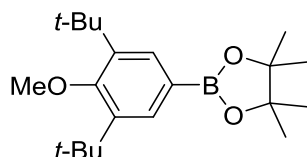
**TLC:**  $R_f = 0.45$  ( $\text{SiO}_2$ , hexane, UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.34 (s, 2H, ar-*H*), 3.69 (s, 3H,  $\text{OCH}_3$ ), 1.41 (s, 18H,  $\text{C}(\text{CH}_3)_3$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 158.9 (s, ar-C-OCH<sub>3</sub>), 146.2 (s, ar-C-C(CH<sub>3</sub>)<sub>3</sub>), 129.7 (s, ar-C), 116.5 (s, ar-C-Br), 64.5 (s, OCH<sub>3</sub>), 36.1 (s, C(CH<sub>3</sub>)<sub>3</sub>), 32.0 (s, C(CH<sub>3</sub>)<sub>3</sub>).

Obtained data are in accordance with literature data.<sup>[134]</sup>

## 2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



A solution of 5-bromo-1,3-di-*tert*-butyl-2-methoxybenzene (1.00 g, 3.35 mmol, 1.00 eq.) in THF (8 mL) was cooled to  $-78\text{ }^{\circ}\text{C}$ . *n*-BuLi (5.4 mL, 1.6 M in hexane, 8.64 mmol, 2.60 eq.) was added dropwise. The resulting colorless suspension was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$ . 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.58 mL, 3.35 mmol, 1.00 eq.) was added dropwise. The suspension was allowed to warm slowly to room temperature and stirred for 14 h. The colorless solution was quenched with EtOH (3 mL) and all volatiles were evaporated under reduced pressure. The residue was taken up in  $\text{CH}_2\text{Cl}_2$  (30 mL) and  $\text{H}_2\text{O}$  (30 mL) was added. The layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 30\text{ mL}$ ). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated under reduced pressure. Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 20\text{ cm}$ , hexane  $\rightarrow$  hexane:ethyl acetate (10:1)) afforded the product (0.80 g, 2.31 mmol, 69%) as a colorless solid.

$\text{C}_{21}\text{H}_{35}\text{BO}_3$  (346.32 g/mol):

**TLC:**  $R_f$  = 0.63 ( $\text{SiO}_2$ , hexane:ethyl acetate (20:1), UV).

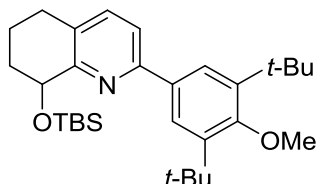
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.71 (s, 2H, ar-*H*), 3.69 (s, 3H, OCH<sub>3</sub>), 1.46 (s, 18H,  $2 \times \text{C}(\text{CH}_3)_3$ ), 1.34 (s, 12H,  $4 \times \text{CH}_3$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 162.7 (s, ar-C), 143.1 (s, ar-C), 133.5 (s, ar-C), 83.6 (s, COB), 64.4 (s, OCH<sub>3</sub>), 35.8 (s,  $\text{C}(\text{CH}_3)_3$ ), 32.3 (s,  $\text{C}(\text{CH}_3)_3$ ), 25.0 (s,  $\text{CH}_3$ ).

Obtained data are in accordance with literature data.<sup>[135]</sup>

## General procedure: Suzuki–Miyaura cross couplings GP1

### 8-((*tert*-Butyldimethylsilyl)oxy)-2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline (2.41)



A microwave vial was charged with 8-((*tert*-butyldimethylsilyl)oxy)-2-chloro-5,6,7,8-tetrahydroquinoline (0.70 g, 2.35 mmol, 1.00 eq.), 2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.22 g, 3.52 mmol, 1.50 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (50 mg, 3.0 mol%) and sealed. The vial was purged with argon for 15 min. Afterwards, degassed *i*-PrOH (12 mL) and degassed 4 M NaOH-solution (1.76 mL) were added. The solution was stirred for 18 h at 50 °C. The reaction mixture was allowed to cool to room temperature, the resulting dark gel was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and H<sub>2</sub>O (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure to afford a dark solid. Purification by column chromatography (SiO<sub>2</sub>, d × h: 3 × 12 cm, hexane:CH<sub>2</sub>Cl<sub>2</sub> (4:1)) afforded the product (1.10 g, 2.28 mmol, 97%) as a colorless solid.

C<sub>30</sub>H<sub>47</sub>NO<sub>2</sub>Si (481.80 g/mol):

**MP:** 107–108 °C.

**TLC:** R<sub>f</sub> = 0.60 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.91 (s, 2H, ar-*H*), 7.51 (d, *J*<sub>HH</sub> = 8.0 Hz, 1H, ar-*H*), 7.42 (d, *J*<sub>HH</sub> = 8 Hz, 1H, ar-*H*), 4.92 (t, *J*<sub>HH</sub> = 3.5 Hz, 1H, CHOSi), 3.74 (s, 3H, OCH<sub>3</sub>), 2.89–2.83 (m, 1H, CH<sub>2</sub>), 2.72–2.68 (m, 1H, CH<sub>2</sub>), 2.23–2.16 (m, 1H, CH<sub>2</sub>), 2.14–2.09 (m, 1H, CH<sub>2</sub>), 1.92–1.82 (m, 1H, CH<sub>2</sub>), 1.79–1.75 (m, 1H, CH<sub>2</sub>), 1.52 (s, 18H, 2 × C(CH<sub>3</sub>)<sub>3</sub>), 0.94 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 0.36 and 0.12 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>).

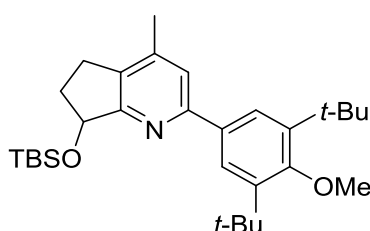
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 160.4 (s, ar-C), 156.9 (s, ar-C), 155.3 (s, ar-C), 143.8 (s, ar-C), 137.8 (s, ar-C), 134.0 (s, ar-C), 130.1 (s, ar-C), 125.5 (s, ar-C), 119.2 (s, ar-C), 70.1 (s, CHOSi), 64.4 (s, OCH<sub>3</sub>), 36.1 (s, C(CH<sub>3</sub>)<sub>3</sub>), 32.5 (s, CH<sub>2</sub>), 32.3 (s, C(CH<sub>3</sub>)<sub>3</sub>), 28.4 (s, CH<sub>2</sub>), 26.1 (s, C(CH<sub>3</sub>)<sub>3</sub>), 18.4 (s, C(CH<sub>3</sub>)), 17.5 (s, CH<sub>2</sub>), –3.6 and –4.6 (s, Si(CH<sub>3</sub>)<sub>2</sub>).

**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 2954 (s), 2867 (m), 1593 (w), 1473 (m), 1412 (m), 1359 (m), 1247 (m), 1221 (m), 1081 (m), 993 (m), 833 (m), 776 (m).

**MS** (FAB NBA):  $m/z$  (%): 484.4 (11), 483.3 (37), 482.3 (94), 481.3 (11), 480.3 (10), 466.3 (10), 426.2 (11), 425.2 (34), 424.2 (100), 350.3 (26), 348.2 (14), 73.1 (28), 57.1 (14).

**EA** ( $\text{C}_{30}\text{H}_{47}\text{NO}_2\text{Si}$ ): calc.: C 74.79, H 9.83, N 2.91; found: C 74.60, H 9.89, N 2.93.

**7-((*tert*-Butyldimethylsilyl)oxy)-2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (2.38)**



The reaction was set up as described in the general procedure **GP1** except using 7-((*tert*-butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (600 mg, 2.01 mmol, 1.00 eq.), 2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.00 g, 2.88 mmol, 1.40 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (40.0 mg, 3.0 mol%), *i*-PrOH (12 mL) and 4 M NaOH-solution (1.5 mL). Extraction and column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $6 \times 21$  cm, hexane: $\text{CH}_2\text{Cl}_2$  (20:1)) afforded the product (840 mg, 1.77 mmol, 88%) as a colorless solid.

$\text{C}_{30}\text{H}_{47}\text{NO}_2\text{Si}$  (481.80 g/mol):

**MP**: 84-87 °C.

**TLC**:  $R_f$  = 0.78 ( $\text{SiO}_2$ , hexane:ethyl acetate (5:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.94 (s, 2H, ar-*H*), 7.33 (s, 1H, ar-*H*), 5.24 (dd,  $J_{\text{HH}}$  = 6.4 Hz,  $J_{\text{HH}}$  = 5.1 Hz, 1H,  $\text{CHOSi}$ ), 3.72 (s, 3H,  $\text{OCH}_3$ ), 3.03-2.96 (m, 1H,  $\text{CH}_2$ ), 2.74-2.67 (m, 1H,  $\text{CH}_2$ ), 2.49-2.42 (m, 1H,  $\text{CH}_2$ ), 2.31 (s, 3H,  $\text{CH}_3$ ), 2.09-2.00 (m, 1H,  $\text{CH}_2$ ), 1.49 (s, 18H,  $2 \times \text{C}(\text{CH}_3)_3$ ), 0.99 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 0.30 and 0.22 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 164.0 (s, ar-*C*), 160.3 (s, ar-*C*), 157.1 (s, ar-*C*), 143.8 (s, ar-*C*), 143.7 (s, ar-*C*), 134.3 (s, ar-*C*), 133.5 (s, ar-*C*), 125.6 (s, ar-*C*), 120.1 (s, ar-*C*), 76.6 (s,  $\text{HCOSi}$ ), 64.4 (s,  $\text{OCH}_3$ ), 36.1 (s,  $2 \times \text{C}(\text{CH}_3)_3$ ), 33.9 (s,  $\text{CH}_2$ ), 32.3 (s,  $2 \times \text{C}(\text{CH}_3)_3$ ), 26.2 (s,  $\text{C}(\text{CH}_3)_3$ ), 26.0 (s,  $\text{CH}_2$ ), 18.9 (s,  $\text{CH}_3$ ), 18.8 (s,  $\text{C}(\text{CH}_3)_3$ ), -3.9 and -4.4 (s,  $\text{Si}(\text{CH}_3)_2$ ).

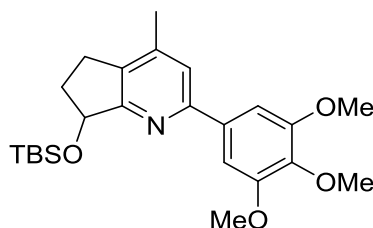


**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 2955 (s), 2856 (m), 1597 (w), 1472 (m), 1406 (m), 1360 (m), 1252 (m), 1218 (m), 1113 (m), 1062 (m), 1001 (m), 912 (w), 867 (m), 836 (m), 778 (m).

**MS** (FAB NBA):  $m/z$  (%): 483.2 (27), 482.2 (64), 481.2 (13), 480.2 (17), 466.2 (11), 425.2 (34), 424.1 (100), 351.1 (12), 350.2 (34), 75.0 (10), 73 (25), 57 (11).

**EA** ( $\text{C}_{30}\text{H}_{47}\text{NO}_2\text{Si}$ ): calc: C 74.79, H 9.83, N 2.91; found: C 74.79, H 9.97, N 2.93.

**7-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-2-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine (2.39)**



The reaction was set up as described in the general procedure **GP1** except using 7-((*tert*-butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (700 mg, 2.35 mmol, 1.00 eq.), (3,4,5-trimethoxyphenyl)boronic acid (850 mg, 4.00 mmol, 1.70 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (50.0 mg, 3.0 mol%), *i*-PrOH (6 mL) and 4 M NaOH-solution (1.76 mL). Extraction and column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $6 \times 32$  cm, hexane:ethyl acetate (4:1)) afforded the product (960 mg, 2.23 mmol, 95%) as a colorless solid.

$\text{C}_{24}\text{H}_{35}\text{NO}_4\text{Si}$  (429.63 g/mol):

**MP**: 88-90 °C.

**TLC**:  $R_f$  = 0.35 ( $\text{SiO}_2$ , hexane:ethyl acetate (4:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.36 (s, 1H, ar-*H*), 7.35 (s, 2H, ar-*H*), 5.25 (dd,  $J_{\text{HH}}$  = 7.2 Hz,  $J_{\text{HH}}$  = 5.7 Hz, 1H,  $\text{HCOSi}$ ), 3.95 (s, 6H,  $2 \times \text{OCH}_3$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 2.95 (ddd,  $J_{\text{HH}}$  = 16.2 Hz,  $J_{\text{HH}}$  = 8.9 Hz,  $J_{\text{HH}}$  = 4.3 Hz, 1H,  $\text{CH}_2$ ), 2.76-2.68 (m, 1H,  $\text{CH}_2$ ), 2.50-2.42 (m, 1H,  $\text{CH}_2$ ), 2.30 (s, 3H,  $\text{CH}_3$ ), 2.07-1.99 (m, 1H,  $\text{CH}_2$ ), 0.99 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 0.27 and 0.23 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ).

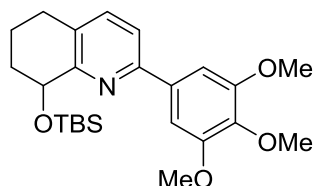
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 164.0 (s, ar-*C*), 155.9 (s, ar-*C*), 153.4 (s, ar-*C*), 144.0 (s, ar-*C*), 138.7 (s, ar-*C*), 135.6 (s, ar-*C*), 134.1 (s, ar-*C*), 119.9 (s, ar-*C*), 104.0 (s, ar-*C*), 76.5 (s,  $\text{COSi}$ ), 61.1 (s,  $\text{OCH}_3$ ), 56.3 (s,  $\text{OCH}_3$ ), 33.9 (s,  $\text{CH}_2$ ), 26.2 (s,  $\text{C}(\text{CH}_3)_3$ ), 25.9 (s,  $\text{CH}_2$ ), 18.9 (s,  $\text{CH}_3$ ), 18.8 (s,  $\text{C}(\text{CH}_3)_3$ ), -4.0 and -4.4 (s,  $\text{Si}(\text{CH}_3)_2$ ).

**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 2996 (m), 2932 (m), 2855 (m), 1586 (m), 1507 (m), 1465 (m), 1444 (m), 1414 (m), 1367 (m), 1357 (m), 1135 (s), 1062 (m), 1083 (w), 910 (w), 839 (w), 766 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 429.2 (2)  $[\text{M}]^+$ , 372.2 (100)  $[\text{M}-\text{C}(\text{CH}_3)_3]^+$ .

**EA** ( $\text{C}_{24}\text{H}_{35}\text{NO}_4\text{Si}$ ): calc.: 67.10, H 8.21, N 3.26; found: 68.92, H 8.29, N 3.37.

**8-((*tert*-Butyldimethylsilyl)oxy)-2-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydroquinoline (2.42)**



The reaction was set up described as in the general procedure **GP1** except using 8-((*tert*-butyldimethylsilyl)oxy)-2-chloro-5,6,7,8-tetrahydroquinoline (350 mg, 1.18 mmol, 1.00 eq.), (3,4,5-trimethoxyphenyl)boronic acid (400 mg, 1.88 mmol, 1.60 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (25 mg, 3 mol%), *i*-PrOH (3 mL) and 4 M NaOH-solution (0.88 mL). Extraction, column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 21$  cm, hexane:ethyl acetate (10:1  $\rightarrow$  1:3)) and recrystallization from hexane afforded the product (455 mg, 1.07 mmol, 91%) as a colorless solid.

$\text{C}_{24}\text{H}_{35}\text{NO}_4\text{Si}$  (429.63 g/mol):

**MP**: 97-99 °C.

**TLC**:  $R_f$  = 0.30 ( $\text{SiO}_2$ , hexane:ethyl acetate (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.53 (d,  $J_{\text{HH}}$  = 8.0 Hz, 1H, ar-*H*), 7.43 (d,  $J_{\text{HH}}$  = 8.0 Hz, 1H, ar-*H*), 7.32 (s, 2H, ar-*H*), 4.88 (s br, 1H,  $\text{CHOSi}$ ), 3.95 (s, 6H,  $2 \times \text{OCH}_3$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 2.88-2.81 (m, 1H,  $\text{CH}_2$ ), 2.75-2.67 (m, 1H,  $\text{CH}_2$ ), 2.18-2.05 (m, 2H,  $\text{CH}_2$ ), 1.93-1.85 (m, 1H,  $\text{CH}_2$ ), 1.79-1.74 (m, 1H,  $\text{CH}_2$ ), 0.91 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 0.30 and 0.11 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ).

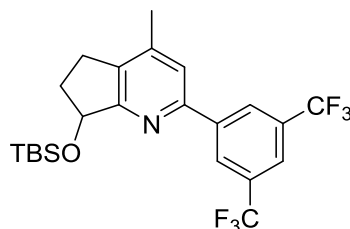
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 157.0 (s, ar-C), 154.0 (s, ar-C), 153.7 (s, ar-C), 138.8 (s, ar-C), 137.9 (s, ar-C), 135.3 (s, ar-C), 130.9 (s, ar-C), 111.8 (s, ar-C), 104.0 (s, ar-C), 70.1 (s,  $\text{OCH}_3$ ), 61.1 (s,  $\text{OCH}_3$ ), 56.3 (s,  $\text{COSi}$ ), 32.6 (s,  $\text{CH}_2$ ), 28.4 (s,  $\text{CH}_2$ ), 26.1 (s,  $\text{C}(\text{CH}_3)_3$ ), 18.5 (s,  $\text{C}(\text{CH}_3)_3$ ), 17.6 (s,  $\text{CH}_2$ ). -3.7 and -4.6 (s,  $\text{Si}(\text{CH}_3)_2$ ).

**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 2998 (m), 2935 (s), 1593 (m), 1564 (m), 1468 (s), 1339 (m), 1233 (m), 1130 (s), 1082 (m), 1031 (m), 1005 (m), 833 (m), 775 (m), 686 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 429.2 (1)  $[\text{M}]^+$ , 372.2 (100)  $[\text{M}-\text{C}(\text{CH}_3)_3]^+$ .

**EA** ( $\text{C}_{24}\text{H}_{35}\text{NO}_4\text{Si}$ ): calc.: C 67.10, H 8.21, N 3.26; found: C 67.28 H 8.34, N 3.42.

**2-(3,5-Bis(trifluoromethyl)phenyl)-7-((*tert*-butyldimethylsilyl)oxy)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (2.40)**



The reaction was setup as described in the general procedure **GP1** except using 7-((*tert*-butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (350 mg, 1.18 mmol, 1.00 eq.), (3,5-bis(trifluoromethyl)phenyl)boronic acid (608 mg, 2.35 mmol, 2.00 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (35.0 mg, 4.0 mol%), *i*-PrOH (3 mL) and 4 M NaOH-solution (0.88 mL). Extraction and column chromatography (SiO<sub>2</sub>, d × h: 3 × 13 cm, hexane:CH<sub>2</sub>Cl<sub>2</sub> (4:1)) afforded the product (484 mg, 1.01 mmol, 86%) as a colorless solid.

C<sub>23</sub>H<sub>27</sub>F<sub>6</sub>NO<sub>4</sub>Si (475.55 g/mol):

**MP:** 115-116 °C.

**TLC:** R<sub>f</sub> = 0.45 (SiO<sub>2</sub>, hexane:CH<sub>2</sub>Cl<sub>2</sub> (3:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 8.58 (s, 2H, ar-*H*), 7.87 (s, 1H, ar-*H*), 7.50 (s, 1H, ar-*H*), 5.27 (dd, *J*<sub>HH</sub> = 7.1 Hz, *J*<sub>HH</sub> = 6.1 Hz, 1H, CHOSi), 3.01 (ddd, *J*<sub>HH</sub> = 16.4 Hz, *J*<sub>HH</sub> = 8.9 Hz, *J*<sub>HH</sub> = 4.0 Hz, 1H, CH<sub>2</sub>), 2.78-2.70 (m, 1H, CH<sub>2</sub>), 2.52 (dddd, *J*<sub>HH</sub> = 12.6 Hz, *J*<sub>HH</sub> = 8.3 Hz, *J*<sub>HH</sub> = 7.5 Hz, *J*<sub>HH</sub> = 4.1 Hz, 1H, CH<sub>2</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 2.10-2.02 (m, 1H, CH<sub>2</sub>), 1.02 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 0.26 and 0.24 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 165.0 (s, ar-*C*), 152.9 (s, ar-*C*), 144.8 (s, ar-*C*), 141.9 (s, ar-*C*), 135.9 (s, ar-*C*), 132.0 (q, *J*<sub>CF</sub> = 33 Hz, ar-*C*), 126.8 (s, ar-*C*), 123.7 (q, *J*<sub>CF</sub> = 273 Hz, CF<sub>3</sub>), 121.9 (sept, *J*<sub>CF</sub> = 3 Hz, ar-*C*), 120.3 (s, ar-*C*), 76.2 (s, COSi), 34.0 (s, CH<sub>2</sub>), 26.0 (s, C(CH<sub>3</sub>)<sub>3</sub>), 25.9 (s, CH<sub>2</sub>), 18.9 (s, CH<sub>3</sub>), 18.8 (s, C(CH<sub>3</sub>)), -4.3 and -4.4 (s, Si(CH<sub>3</sub>)<sub>2</sub>).

**<sup>19</sup>F{<sup>1</sup>H} NMR** (376 MHz, CDCl<sub>3</sub>): δ/ppm = -63.2 (s).

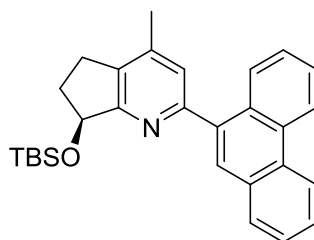
**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 2956 (m), 2935 (m), 2857 (m), 1600 (w), 1391 (m), 1375 (w), 1349 (w), 1319 (m), 1282 (s), 1254 (m), 1282 (s), 1254 (m), 1179 (s), 1125 (s), 942 (w), 915 (w), 894 (m), 858 (m), 781 (m), 683 (m).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 418.1 (100) [M-C(CH<sub>3</sub>)<sub>3</sub>]<sup>+</sup>, 344.1 (13) [M-OTBS]<sup>+</sup>, 75.1 (9).

**MS** (FAB NBA):  $m/z$  (%): 476.2 (30)  $[M+1]^+$ , 418.1 (100)  $[M-C(CH_3)_3]^+$ , 344.1 (49)  $[M-OTBS]^+$ , 73.1 (26).

**EA** ( $C_{23}H_{27}F_6NOSi$ ): calc.: C 58.09, H 5.72, N 2.95; found: C 57.97, H 5.72, N 3.08.

**(*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-2-(phenanthren-9-yl)-6,7-dihydro-5H-cyclopenta[*b*]pyridine ((*S*)-2.43)**



The reaction was setup as described in the general procedure **GP1** except using (*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine (200 mg, 0.67 mmol, 1.00 eq.), 9-phenanthracenylboronic acid (224 mg, 1.01 mmol, 1.50 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (17.0 mg, 4.0 mol%), *i*-PrOH (3.5 mL) and 4 M NaOH-solution (0.50 mL). Extraction and column chromatography ( $SiO_2$ , d  $\times$  h: 3  $\times$  25 cm, pentane:Et<sub>2</sub>O (20:1)) afforded the product (295 mg, 0.67 mmol, quant.) as a colorless solid.

$C_{29}H_{33}NOSi$  (439.67 g/mol):

**MP**: 159-160 °C.

**TLC**:  $R_f$  = 0.56 ( $SiO_2$ , pentane:Et<sub>2</sub>O (10:1), UV).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 8.77 (d,  $J$  = 8.3 Hz, 1H, ar-*H*), 8.73 (d,  $J$  = 8.2 Hz, 1H, ar-*H*), 8.36 (dd,  $J$  = 8.4, 1.4 Hz, 1H, ar-*H*), 7.91 (dd,  $J$  = 7.8, 1.1 Hz, 1H, ar-*H*), 7.86 (s, 1H, ar-*H*), 7.71-7.64 (m, 2H, ar-*H*), 7.64-7.58 (m, 1H, ar-*H*), 7.54 (ddd,  $J$  = 8.2, 7.0, 1.1 Hz, 1H, ar-*H*), 7.33 (s, 1H, ar-*H*), 5.28 (dd,  $J$  = 6.9, 4.2 Hz, 1H, *CHOSi*), 3.16-3.06 (m, 1H, *CH*<sub>2</sub>), 2.87-2.76 (m, 1H, *CH*<sub>2</sub>), 2.55-2.43 (m, 1H, *CH*<sub>2</sub>), 2.37 (s, 3H, *CH*<sub>3</sub>), 2.18-2.07 (m, 1H, *CH*<sub>2</sub>), 0.96 (s, 9H, *C*(*CH*<sub>3</sub>)<sub>3</sub>), 0.21 and 0.17 (s, 6H, *Si*(*CH*<sub>3</sub>)<sub>2</sub>).

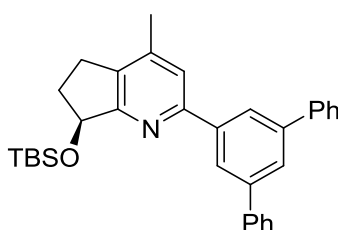
**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 164.0 (s, ar-*C*), 158.4 (s, ar-*C*), 144.0 (s, ar-*C*), 137.8 (s, ar-*C*), 134.3 (s, ar-*C*), 131.7 (s, ar-*C*), 130.9 (s, ar-*C*), 130.5 (s, ar-*C*), 130.5 (s, ar-*C*), 129.0 (s, ar-*C*), 128.6 (s, ar-*C*), 127.6 (s, ar-*C*), 126.9 (s, ar-*C*), 126.8 (s, ar-*C*), 126.5 (s, ar-*C*), 126.5 (s, ar-*C*), 125.1 (s, ar-*C*), 122.8 (s, ar-*C*), 122.7 (s, ar-*C*), 76.6 (s, *COSi*), 34.0 (s, *CH*<sub>2</sub>), 26.2 (s, *CH*<sub>2</sub>), 26.1 (s, *C*(*CH*<sub>3</sub>)<sub>3</sub>), 18.9 (s, *CH*<sub>3</sub>), 18.7 (s, *C*(*CH*<sub>3</sub>)<sub>3</sub>), -4.0 and -4.4 (s, *Si*(*CH*<sub>3</sub>)<sub>2</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3062 (w), 2951 (m), 2852 (m), 2361 (w), 1596 (m), 1459 (m), 1381 (m), 1297 (w), 1249 (m), 1082 (s), 992 (m), 924 (m), 837 (s), 769 (s), 745 (s), 684 (m).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{29}\text{H}_{34}\text{NOSi}^+$ : 440.2404  $[\text{M}+\text{H}]^+$ ; found: 440.2403.

$[\alpha]_D^{20} = -85.4$  ( $c = 0.60$ ,  $\text{CHCl}_3$ ).

**(S)-2-([1,1':3',1''-Terphenyl]-5'-yl)-7-((*tert*-butyldimethylsilyl)oxy)-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine ((S)-2.42)**



The reaction was set up as described in the general procedure **GP1** except using (*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine (200 mg, 0.67 mmol, 1.00 eq.), (3,5-diphenylphenyl)boronic acid (276 mg, 1.01 mmol, 1.50 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (17.0 mg, 4 mol%), *i*-PrOH (3.5 mL) and 4 M NaOH-solution (0.5 mL). Extraction and column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 25$  cm, pentane:Et<sub>2</sub>O (20:1)) afforded the product (197 mg, 0.40 mmol, 60%) as a colorless solid.

$\text{C}_{33}\text{H}_{45}\text{NOSi}$  (491.75 g/mol):

**MP**: 124-125 °C.

**TLC**:  $R_f = 0.53$  ( $\text{SiO}_2$ , pentane:Et<sub>2</sub>O (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.31 (d,  $J = 1.8$  Hz, 2H, ar-*H*), 7.83 (t,  $J = 1.8$  Hz, 1H, ar-*H*), 7.78-7.71 (m, 4H, ar-*H*), 7.54 (s, 1H, ar-*H*), 7.53-7.45 (m, 4H, ar-*H*), 7.43-7.35 (m, 2H, ar-*H*), 5.28 (dd,  $J = 7.2, 5.3$  Hz, 1H, CHOSi), 3.08-2.97 (m, 1H,  $\text{CH}_2$ ), 2.79-2.68 (m, 1H,  $\text{CH}_2$ ), 2.57-2.43 (m, 1H,  $\text{CH}_2$ ), 2.34 (s, 3H,  $\text{CH}_3$ ), 2.14-1.99 (m, 1H,  $\text{CH}_2$ ), 1.01 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 0.29 (s, 3H Si( $\text{CH}_3$ )), 0.25 (s, 3H Si( $\text{CH}_3$ )).

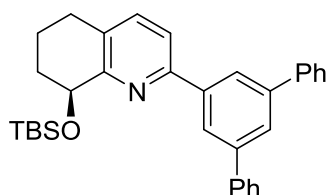
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 164.2 (s, ar-*C*), 156.0 (s, ar-*C*), 144.0 (s, ar-*C*), 142.0 (s, ar-*C*), 141.3 (s, ar-*C*), 140.8 (s, ar-*C*), 134.3 (s, ar-*C*), 128.8 (s, ar-*C*), 127.4 (s, ar-*C*), 127.3 (s, ar-*C*), 126.0 (s, ar-*C*), 124.8 (s, ar-*C*), 120.3 (s, ar-*C*), 76.4 (s, COSi), 33.9 (s,  $\text{CH}_2$ ), 26.1 (s,  $\text{C}(\text{CH}_3)_3$ ), 25.8 (s,  $\text{CH}_2$ ), 18.8 (s,  $\text{CH}_3$ ), 18.7 (s,  $\text{C}(\text{CH}_3)_3$ ), -4.2 and -4.5 (s, Si( $\text{CH}_3$ )<sub>2</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3063 (w), 2953 (m), 2854 (m), 2056 (w), 1595 (m), 1469 (m), 1407 (m), 1346 (w), 1245 (m), 1118 (m), 1008 (w), 836 (s), 758 (s), 697 (s).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{33}\text{H}_{38}\text{NOSi}^+$ : 492.2717  $[\text{M}+\text{H}]^+$ ; found: 492.2720.

$[\alpha]_D^{20} = +2.8$  ( $c = 0.25$ ,  $\text{CHCl}_3$ ).

**(S)-2-([1,1':3',1''-Terphenyl]-5'-yl)-8-((*tert*-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydroquinoline ((S)-2.45)**



The reaction was set up as described in the general procedure **GP1** except using (*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-chloro-5,6,7,8-tetrahydroquinoline (200 mg, 0.67 mmol, 1.00 eq.), (3,5-diphenylphenyl)boronic acid (282 mg, 1.03 mmol, 1.50 eq. allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (25.0 mg, 4 mol%), *i*-PrOH (3.5 mL) and 4 M NaOH-solution (0.5 mL). Extraction and column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 25$  cm, pentane: $\text{Et}_2\text{O}$  (20:1)) afforded the product (282 mg, 0.57 mmol, 83%) as a colorless solid.

$\text{C}_{33}\text{H}_{37}\text{NOSi}$  (491.75 g/mol):

**MP**: 51-52 °C.

**TLC**:  $R_f = 0.78$  ( $\text{SiO}_2$ , pentane: $\text{Et}_2\text{O}$  (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.32 (d,  $J = 1.7$  Hz, 2H, ar-*H*), 7.87 (t,  $J = 1.7$  Hz, 1H, ar-*H*), 7.80-7.74 (m, 4H, ar-*H*), 7.71 (d,  $J = 8.0$  Hz, 1H, ar-*H*), 7.56-7.47 (m, 5H, ar-*H*), 7.46-7.38 (m, 2H, ar-*H*), 4.96 (t,  $J = 4.1$  Hz, 1H,  $\text{CHOSi}$ ), 2.93-2.86 (m, 1H,  $\text{CH}_2$ ), 2.84-2.70 (m, 1H,  $\text{CH}_2$ ), 2.26-2.06 (m, 2H,  $\text{CH}_2$ ), 2.00-1.93 (m, 1H,  $\text{CH}_2$ ), 1.85-1.77 (m, 1H,  $\text{CH}_2$ ), 0.97 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 0.35 and 0.18 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 157.2 (s, ar-C), 154.2 (s, ar-C), 142.1 (s, ar-C), 141.3 (s, ar-C), 140.6 (s, ar-C), 137.8 (s, ar-C), 131.2 (s, ar-C), 128.8 (s, ar-C), 127.5 (s, ar-C), 127.4 (s, ar-C), 126.3 (s, ar-C), 124.7 (s, ar-C), 119.1 (s, ar-C), 70.1 ( $\text{CHOSi}$ ), 32.6 (s,  $\text{CH}_2$ ), 28.4 (s,  $\text{CH}_2$ ), 26.0 (s,  $\text{C}(\text{CH}_3)_3$ ), 18.5 (s,  $\text{C}(\text{CH}_3)_3$ ), 17.7 (s,  $\text{CH}_2$ ), -3.8 and -4.6 (s,  $\text{Si}(\text{CH}_3)_2$ ).

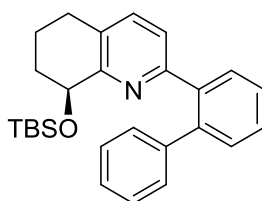
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3060 (w), 3033 (w), 2927 (m), 2853 (m), 1594 (m), 1564 (m), 1498 (m), 1471 (m), 1454 (m), 1436 (m), 1410 (m), 1387 (m), 1358 (m), 1249 (w), 1190 (w), 1153 (m), 1080 (m), 1048 (m), 1027 (w), 1005 (m), 990 (m), 938 (w), 880 (m), 871 (m), 831 (s), 806 (m), 775 (s), 755 (s), 696 (s), 613 (m).

**MS** (ESI, MeOH)  $m/z$  (%): 492  $[\text{M}+\text{H}]^+$ .

**EA** ( $\text{C}_{33}\text{H}_{37}\text{NOSi}$ ): calc.: C 80.60, H 7.58, N 2.85; found: C 80.54, H 7.58, N 3.00.

$[\alpha]_D^{20} = +26.7$  ( $c = 0.52$ ,  $\text{CHCl}_3$ ).

**(S)-((7-([1,1'-Biphenyl]-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)(tert-butyl) dimethyl silane ((S)-2.46)**



The reaction was set up as described in the general procedure **GP1** except using (S)-8-((tert-butyltrimethylsilyl)oxy)-2-chloro-5,6,7,8-tetrahydroquinoline (400 mg, 1.35 mmol, 1.00 eq.), [1,1'-biphenyl]-3-ylboronic acid (402 mg, 2.03 mmol, 1.50 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (25.0 mg, 4 mol%), *i*-PrOH (7.0 mL) and 4 M NaOH-solution (1.0 mL). Extraction and column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $25 \times 3$  cm, cyclohexane:ethyl acetate (50:1)) afforded the product (200 mg, 0.49 mmol, 36%) as a colorless resin.

$\text{C}_{27}\text{H}_{33}\text{NOSi}$  (415.65 g/mol):

**TLC**:  $R_f = 0.35$  ( $\text{SiO}_2$ , cyclohexane:ethyl acetate (50:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.85-7.83 (m, 1H, ar-*H*), 7.48-7.39 (m, 3H, ar-*H*), 7.28-7.24 (m, 3H, ar-*H*), 7.24-7.19 (m, 2H, ar-*H*), 7.01 (d,  $^3J_{\text{HH}} = 8.0$  Hz, 1H, ar-*H*), 6.59 (d,  $^3J_{\text{HH}} = 8.0$  Hz, 1H, ar-*H*), 4.88 (t,  $^3J_{\text{HH}} = 4.8$  Hz, 1H, *HCOSi*), 2.79-2.72 (m, 1H,  $\text{CH}_2$ ), 2.67-2.59 (m, 1H,  $\text{CH}_2$ ), 2.16-2.04 (m, 2H,  $\text{CH}_2$ ), 1.97-1.89 (m, 1H,  $\text{CH}_2$ ), 1.78-1.70 (m, 1H,  $\text{CH}_2$ ), 0.92 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 0.25 (s, 3H,  $\text{SiCH}_3$ ), 0.11 (s, 3H,  $\text{SiCH}_3$ ).

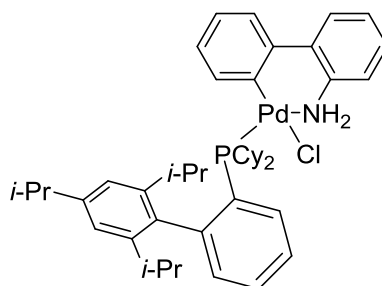
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 157.0 (s, ar-*C*), 155.8 (s, ar-*C*), 141.8 (s, ar-*C*), 140.5 (s, ar-*C*), 139.6 (s, ar-*C*), 135.8 (s, ar-*C*), 131.0 (s, ar-*C*), 130.4 (s, ar-*C*), 129.8 (s, ar-*C*), 128.1 (s, ar-*C*), 128.0 (s, ar-*C*), 127.4 (s, ar-*C*), 126.6 (s, ar-*C*), 124.2 (s, ar-*C*), 70.1 (s, *COSi*), 32.5 (s,  $\text{CH}_2$ ), 28.2 (s,  $\text{CH}_2$ ), 26.9 (s,  $\text{CH}_2$ ), 26.0 (s,  $\text{C}(\text{CH}_3)_3$ ), 17.7 (s,  $\text{C}(\text{CH}_3)_3$ ), -3.9 and -4.8 (s,  $\text{Si}(\text{CH}_3)_2$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3062 (w), 2951 (m), 2852 (m), 2361 (w), 1596 (m), 1459 (m), 1381 (m), 1297 (w), 1249 (m), 1082 (s), 992 (m), 924 (m), 837 (s), 769 (s), 745 (s), 684 (m).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{27}\text{H}_{34}\text{NOSi}^+$ : 416.2404  $[\text{M}+\text{H}]^+$ ; found: 416.2408.

$[\alpha]_D^{20} = +22.6$  ( $c = 0.48$ ,  $\text{CHCl}_3$ ).

### Palladium complex (2.49)



A mixture of  $\text{Pd}(\text{OAc})_2$  (100 mg, 0.45 mmol, 1.00 eq.) and 2-amino-biphenyl (78 mg, 0.46 mmol, 1.00 eq.) in toluene (2.7 mL) was stirred for 45 min at 60 °C under an argon atmosphere, whereupon a grey precipitate had formed. After cooling to room temperature, toluene was decanted. The remaining solid was washed with toluene ( $3 \times 1.0$  mL) and suspended in acetone (2.7 mL). After addition of lithium chloride (57 mg, 1.34 mmol, 3.00 eq.), the reaction mixture was stirred for 1 h at room temperature. XPhos (202 mg, 0.42 mmol, 0.95 eq.) was added in small portions and the mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure to afford a yellow slurry, which was treated with MTBE (0.6 mL) and pentane (1.5 mL). The mixture was placed in the refrigerator (4 °C) overnight. The product was then collected by filtration, washed with  $\text{H}_2\text{O}$  ( $3 \times 1.0$  mL), and dried under reduced pressure to afford the palladium complex as a grey solid (219 mg, 280  $\mu\text{mol}$ , 62%).

$\text{C}_{45}\text{H}_{59}\text{ClNPPd}$  (786.82 g/mol):

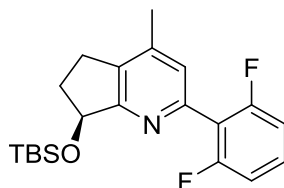
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = complex spectrum, identic to literature.

$^{31}\text{P}\{^1\text{H}\}$  NMR (161 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 66.8 (s), 64.1 (s), (rotamers).

Obtained data are in accordance with literature data.<sup>[62]</sup>



**(S)-7-((*tert*-Butyldimethylsilyl)oxy)-2-(2,6-difluorophenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine ((S)-2.44)**



(S)-7-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine (250 mg, 0.84 mmol, 1.00 eq.), (2,6-difluorophenyl)boronic acid (199 mg, 1.26 mmol, 1.50 eq.) and the palladium complex (**2.49**) (20 mg, 3 mol%) were added to a microwave vial and sealed. The vessel was evacuated and backfilled with argon for 3 times. Afterwards, degassed THF (1.7 mL) and degassed 0.5 M  $K_3PO_4$ -solution (3.4 mL) were added. The solution was stirred for 1 h at room temperature.  $Et_2O$  (10 mL) and  $H_2O$  (10 mL) were added and the aqueous phase was extracted with  $Et_2O$  ( $3 \times 10$  mL). The organic phase was dried over  $MgSO_4$ , all volatiles evaporated under reduced pressure and the residue was purified by column chromatography ( $SiO_2$ ,  $d \times h$ :  $3 \times 23$  cm, pentane: $Et_2O$  (20:1)) to afford the product (300 mg, 0.80 mmol, 95%) as a colorless solid.

$C_{21}H_{27}F_2NOSi$  (375.53 g/mol):

**MP:** 45-46 °C.

**TLC:**  $R_f$  = 0.69 ( $SiO_2$ , pentane: $Et_2O$  (4:1), UV).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 7.34-7.26 (tt,  $J$  = 8.4, 6.0 Hz, 1H, ar-*H*), 7.13 (s, 1H, ar-*H*), 7.01-6.92 (m, 2H, ar-*H*), 5.22 (dd,  $J$  = 6.8, 4.2 Hz, 1H, *CHOSi*), 3.04 (ddd,  $J$  = 16.2, 8.5, 5.8 Hz, 1H,  $CH_2$ ), 2.74 (ddd,  $J$  = 16.2, 8.5, 5.1 Hz, 1H,  $CH_2$ ), 2.49-2.36 (m, 1H,  $CH_2$ ), 2.31 (s, 3H,  $CH_3$ ), 2.13-2.02 (m, 1H,  $CH_2$ ), 0.92 (s, 9H,  $C(CH_3)_3$ ), 0.21 and 0.11 (s, 6H,  $Si(CH_3)_2$ ).

**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 164.4 (s, ar-C), 160.8 (dd,  $J_{CF}$  = 250, 7.0 Hz, ar-C), 148.0 (s, ar-C), 143.6 (s, ar-C), 135.3 (s, ar-C), 129.5 (t,  $J_{CF}$  = 10 Hz, ar-C), 125.8 (s, ar-C), 118.9 (t,  $J_{CF}$  = 18 Hz, ar-C), 112.7-109.9 (m, ar-C), 76.5 (s, *COSi*), 33.9 (s,  $CH_2$ ), 26.2 (s,  $CH_2$ ), 26.1 (s,  $C(CH_3)_3$ ), 18.7 (s,  $CH_3$ ), 18.6 (s,  $C(CH_3)_3$ ), -4.2 and -4.6 (s,  $Si(CH_3)_2$ ).

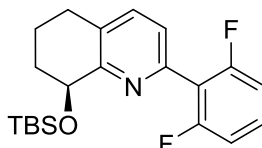
**$^{19}F\{^1H\}$  NMR** (376 MHz,  $CDCl_3$ ):  $\delta/ppm$  = -114.0.

**IR** (ATR):  $\tilde{\nu}/cm^{-1}$  = 2929 (w), 2856 (w), 1628 (m), 1596 (w), 1465 (m), 1358 (w), 1251 (m), 1158 (w), 1116 (m), 1066 (w), 1001 (m), 938 (w), 915 (w), 859 (m), 836 (m), 776 (s), 732 (m), 645 (s).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $C_{21}H_{28}F_2NOSi^+$ : 376.1903  $[M+H]^+$ ; found: 376.1907.

$[\alpha]_D^{20} = +3.4$  ( $c = 1.02$ ,  $CHCl_3$ ).

**(S)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(2,6-difluorophenyl)-5,6,7,8-tetrahydroquinoline ((S)-2.48)**



(S)-8-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-5,6,7,8-tetrahydroquinoline (503 mg, 1.69 mmol, 1.00 eq.), (2,6-difluorophenyl)boronic acid (400 mg, 2.53 mmol, 1.50 eq.) and the palladium complex (**2.49**) (40 mg, 3 mol%) were added to a microwave vial and sealed. The vessel was evacuated and backfilled with argon for 3 times. Afterwards, degassed THF (3.4 mL) and degassed 0.5 M  $K_3PO_4$ -solution (6.8 mL) were added. The solution was stirred for 1 h at room temperature.  $Et_2O$  (20 mL) and water (20 mL) were added and the aqueous phase was extracted with  $Et_2O$  ( $3 \times 20$  mL). The organic phase was dried over  $MgSO_4$ , all volatiles evaporated under reduced pressure and the residue was purified by column chromatography ( $SiO_2$ ,  $d \times h$ :  $3 \times 25$  cm, pentane: $Et_2O$  (50:1)) to afford the product (627 mg, 1.59 mmol, 94%) as a colorless oil.

$C_{21}H_{27}F_2NOSi$  (375.53 g/mol):

**TLC**:  $R_f = 0.40$  ( $SiO_2$ , pentane: $Et_2O$  (50:1), UV).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta/ppm = 7.49$  (d,  $J = 7.9$  Hz, 1H, ar-*H*), 7.41-7.31 (m, 2H, ar-*H*), 7.05-6.93 (m, 2H, ar-*H*), 4.89 (t,  $J = 4.3$  Hz, 1H, OCH), 2.98-2.85 (m, 1H,  $CH_2$ ), 2.85-2.67 (m, 1H,  $CH_2$ ), 2.25-2.03 (m, 2H,  $CH_2$ ), 2.03-1.91 (m, 1H,  $CH_2$ ), 1.88-1.72 (m, 1H,  $CH_2$ ), 0.91 (s, 9H,  $C(CH_3)_3$ ), 0.22 (s, 3H,  $SiCH_3$ ), 0.04 (s, 3H,  $SiCH_3$ ).

**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta/ppm = 160.8$  (dd,  $^1J_{CF} = 250$  Hz,  $^3J_{CF} = 7$  Hz, ar-*C*), 157.8 (s, ar-*qC*), 146.6 (s, ar-*qC*), 137.1 (s, ar-CH), 131.8 (s, ar-*qC*), 129.7 (t,  $^3J_{CF} = 10$  Hz, ar-*qC*), 124.5 (d,  $^3J_{CF} = 2.0$  Hz, ar-CH), 118.6 (t,  $^2J_{CF} = 18.0$  Hz, ar-*qC*), 112.0 (dd,  $J = 18$  Hz,  $J = 8.0$  Hz, ar-CH), 70.2 (s, CHOSi), 32.5 (s,  $CH_2$ ), 28.5 (s,  $CH_2$ ), 26.0 (s,  $C(CH_3)_3$ ), 18.5 (s,  $C(CH_3)_3$ ), 17.9 (s,  $CH_2$ ), -4.3 and -5.0 (s,  $Si(CH_3)_2$ ).

**$^{19}F\{^1H\}$  NMR** (376 MHz,  $CDCl_3$ ):  $\delta/ppm = -119.2$  (s).

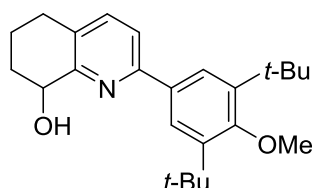
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2930 (m), 2854 (m), 1626 (w), 1467 (s), 1232 (m), 999 (s), 924 (m), 830 (s), 776 (s).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{21}\text{H}_{28}\text{F}_2\text{NOSi}^+$ : 376.1903  $[\text{M}+\text{H}]^+$ ; found: 376.1902.

$[\alpha]_D^{20}$  = +11.3 ( $c$  = 0.92,  $\text{CHCl}_3$ ).

## General procedure: TBS deprotections GP2

### 2-(3,5-di-*tert*-Butyl-4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-8-ol ((*S*)-2.51)



The analogous TBS ether (0.40 g, 0.93 mmol, 1.00 eq.) was dissolved in THF (15 mL) and TBAF  $\times$  3  $\text{H}_2\text{O}$  (1.17 g, 3.72 mmol, 4.00 eq.) was added. The resulting yellow solution was stirred for 4 h at 50 °C. The solvent was evaporated under reduced pressure to obtain a brown oil. This oil was taken up in  $\text{CH}_2\text{Cl}_2$  (30 mL) and washed with  $\text{H}_2\text{O}$  (30 mL). The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 30$  mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated under reduced pressure. The brown residue was purified by column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 11$  cm, hexane:ethyl acetate (20:1  $\rightarrow$  1:1)) to afford the product (0.26 g, 0.82 mmol, 88%) as a colorless solid.

$\text{C}_{24}\text{H}_{33}\text{NO}_2$  (367.53 g/mol):

**MP**: 188-189 °C.

**TLC**:  $R_f$  = 0.49 ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.84 (s, 2H, ar-*H*), 7.51 (d,  $J_{\text{HH}}$  = 8.0 Hz, 1H, ar-*H*), 7.46 (d,  $J_{\text{HH}}$  = 8.0 Hz, 1H, ar-*H*), 4.74 (dd,  $J_{\text{HH}}$  = 9.0 Hz,  $J_{\text{HH}}$  = 4.4 Hz, 1H, *H*COH), 4.34 (s, 1H, OH), 3.72 (s, 3H,  $\text{OCH}_3$ ), 2.91-2.78 (m, 2H,  $\text{CH}_2$ ), 2.40-2.34 (m, 1H,  $\text{CH}_2$ ), 2.06-2.03 (m, 1H,  $\text{CH}_2$ ), 1.91-1.75 (m, 2H,  $\text{CH}_2$ ), 1.49 (s, 18H,  $2 \times \text{C}(\text{CH}_3)_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 160.8 (s, ar-C), 157.6 (s, ar-C), 155.2 (s, ar-C), 144.1 (s, ar-C), 137.8 (s, ar-C), 133.3 (s, ar-C), 129.2 (s, ar-C), 125.4 (s, ar-C), 119.4 (s, ar-C),

69.2 (s, COH), 64.5 (s, OCH<sub>3</sub>), 36.1 (s, C(CH<sub>3</sub>)<sub>3</sub>), 32.2 (s, C(CH<sub>3</sub>)<sub>2</sub>), 30.8 (s, CH<sub>2</sub>), 28.1 (s, CH<sub>2</sub>), 19.8 (s, CH<sub>2</sub>).

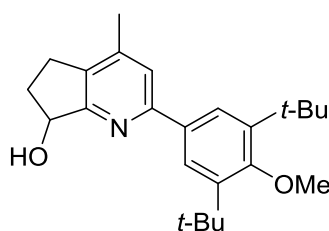
**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 3475 (m), 2944 (s), 2866 (m), 1589 (m), 1472 (m), 1450 (s), 1414 (s), 1248 (m), 1225 (s), 1117 (m), 1066 (m), 1013 (m), 824 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 368.3 (27), 367.3 (100), 366.2 (12), 353.2 (15), 352.2 (59), 339.3 (10), 338.2 (22), 334.2 (21), 311.2 (29), 304.2 (29), 292.2 (10), 278 (11).

**EA** (C<sub>24</sub>H<sub>33</sub>NO<sub>2</sub>): calc.: C 78.43, H 9.05, N 3.81; found: C 78.16, H 9.17, N 3.84.

**HPLC**: *Daicel*, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 13.2 min and 15.6 min.

**2-(3,5-di-*tert*-Butyl-4-methoxyphenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol ((*S*)-2.50)**



The reaction was set up as described in the general procedure **GP2** except using the analogous TBS ether (800 mg, 1.66 mmol, 1.00 eq.) and TBAF × 3 H<sub>2</sub>O (2.09 g, 6.64 mmol, 4.00 eq.) dissolved in THF (8 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d × h: 3 × 15 cm, hexane:ethyl acetate (20:1 → 10:1)) afforded the product (488 mg, 1.48 mmol, 79%) as a colorless solid.

C<sub>24</sub>H<sub>33</sub>NO<sub>2</sub> (367.53 g/mol):

**MP**: 153-155 °C.

**TLC**:  $R_f$  = 0.16 (SiO<sub>2</sub>, hexane:ethyl acetate (5:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta/\text{ppm}$  = 7.77 (s, 2H, ar-*H*), 7.30 (s, 1H, ar-*H*), 5.25 (t,  $J_{\text{HH}}$  = 6.4 Hz, 1H, CHOH), 4.21 (s br, 1H, OH), 3.72 (s, 3H, OCH<sub>3</sub>), 2.96 (ddd,  $J_{\text{HH}}$  = 16.1, 8.9, 4.2 Hz, 1H, CH<sub>2</sub>), 2.77-2.69 (m, 1H, CH<sub>2</sub>), 2.54-2.46 (m, 1H, CH<sub>2</sub>), 2.33 (s, 3H, CH<sub>3</sub>), 2.07-1.99 (m, 1H, CH<sub>2</sub>), 1.47 (s, 18 H, 2 × C(CH<sub>3</sub>)<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta/\text{ppm}$  = 164.2 (s, ar-C), 160.4 (s, ar-C), 157.9 (s, ar-C), 144.5 (s, ar-C), 143.8 (s, ar-C), 134.1 (s, ar-C), 133.6 (s, ar-C), 125.8 (s, ar-C), 121.3 (s, ar-C), 74.9 (s, CHOH), 64.4 (s, OCH<sub>3</sub>), 36.0 (s, 2 × C(CH<sub>3</sub>)<sub>3</sub>), 32.5 (s, CH<sub>2</sub>), 32.2 (s, 2 × C(CH<sub>3</sub>)<sub>3</sub>), 26.0 (s, CH<sub>2</sub>), 18.9 (s, CH<sub>3</sub>).

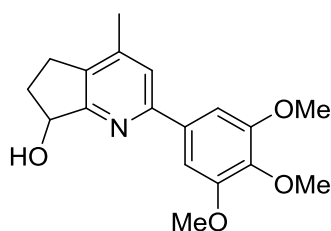
**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 3197 (m, br), 3004 (m), 2960 (s), 1597 (m), 1442 (m), 1405 (m), 1216 (s), 1114 (m), 1002 (m), 867 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 368.3 (26), 367.3 (100), 353.2 (19), 352.2 (75), 334.2 (16), 310.2 (11), 304.2 (27).

**EA** ( $\text{C}_{24}\text{H}_{33}\text{NO}_2$ ): calc.: C 78.43, H 9.05, N 3.81; found: C 78.74, H 9.21, N 3.87.

**HPLC**: *Daicel*, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 11.4 min and 13.3 min.

#### 4-Methyl-2-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (2.52)



The reaction was set up as described in the general procedure **GP2** except using the analogous TBS ether (800 mg, 1.86 mmol, 1.00 eq.) and TBAF  $\times$  3  $\text{H}_2\text{O}$  (2.35 g, 7.44 mmol, 4.00 eq.) dissolved in THF (8 mL). Extraction and purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 15  $\times$  3 cm, hexane:ethyl acetate (10:1  $\rightarrow$  1:3)) afforded the product (482 mg, 1.60 mmol, 86%) as a colorless solid.

$\text{C}_{18}\text{H}_{21}\text{NO}_4$  (315.37 g/mol):

**MP**: 149-151 °C.

**TLC**:  $R_f$  = 0.15 ( $\text{SiO}_2$ , hexane:ethyl acetate (1:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.31 (s, 1H, ar-H), 7.15 (s, 2H, ar-H), 5.25 (dd,  $J_{\text{HH}}$  = 7.2, 5.7 Hz, 1H, HCOH), 5.51 (s br, 1H, OH), 3.86 (s, 9H, 3  $\times$   $\text{OCH}_3$ ), 2.95 (ddd,  $J_{\text{HH}}$  = 16.2, 8.9, 4.3 Hz, 1H,  $\text{CH}_2$ ), 2.76-2.68 (m, 1H,  $\text{CH}_2$ ), 2.54-2.45 (m, 1H,  $\text{CH}_2$ ), 2.32 (s, 3H,  $\text{CH}_3$ ), 2.07-1.99 (m, 1H,  $\text{CH}_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 164.3 (s, ar-C), 156.6 (s, ar-C), 153.4 (s, ar-C), 144.9 (s, ar-C), 138.8 (s, ar-C), 135.2 (s, ar-C), 134.4 (s, ar-C), 121.0 (s, ar-C), 104.4 (s, ar-C), 74.9 (s, COH), 61.0 (s,  $\text{OCH}_3$ ), 56.2 (s,  $\text{OCH}_3$ ), 32.5 (s,  $\text{CH}_2$ ), 26.0 (s,  $\text{CH}_2$ ), 18.9 (s,  $\text{CH}_3$ ).

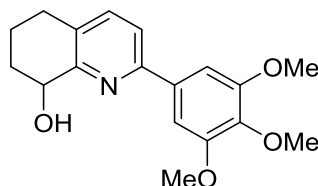
**IR** (KBr):  $\tilde{\nu}/\text{cm}^{-1}$  = 3184 (w, br), 2938 (w), 1585 (m), 1466 (m), 1246 (w), 1230 (w), 1121 (s), 1009 (m), 964 (w), 832 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 315.1 (100), 300.1 (43), 272.1 (12), 242.1 (10).

**EA** ( $\text{C}_{18}\text{H}_{21}\text{NO}_4$ ): calc.: C 68.55, H 6.71, N 4.44; found: C 68.29, H 6.92, N 4.42.

**HPLC:** *Daicel*, Chiralpak AD-H (0.46 cm × 25 cm, heptane/iso-propanol = 85:15, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 30.5 min and 33.4 min.

**2-(3,4,5-Trimethoxyphenyl)-5,6,7,8-tetrahydroquinolin-8-ol (2.53)**



The reaction was set up as described in the general procedure **GP2** except using the analogous TBS ether (400 mg, 0.93 mmol, 1.00 eq.) and TBAF × 3 H<sub>2</sub>O (1.17 g, 3.72 mmol, 4.00 eq.) dissolved in THF (15 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d × h: 3 × 11 cm, hexane:ethyl acetate (20:1 → 1:1)) afforded the product (260 mg, 0.82 mmol, 88%) as a colorless solid.

C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub> (315.37 g/mol):

**MP:** 151-152 °C.

**TLC:**  $R_f$  = 0.40 (SiO<sub>2</sub>, hexane:ethyl acetate (1:1), UV).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.52 (d,  $J_{HH}$  = 6.4 Hz, 1H, ar-*H*), 7.48 (d,  $J_{HH}$  = 6.4 Hz, 1H, ar-*H*), 7.21 (s, 2H, ar-*H*), 4.74 (dd,  $J_{HH}$  = 9.0, 5.0 Hz, 1H, HCOH), 4.28 (s, 1H, COH), 3.95 (s, 6H, 2 × OCH<sub>3</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 2.90-2.80 (m, 2H, CH<sub>2</sub>), 2.38-2.34 (m, 1H, CH<sub>2</sub>), 2.07-2.01 (m, 1H, CH<sub>2</sub>), 1.90-1.77 (m, 2H, CH<sub>2</sub>).

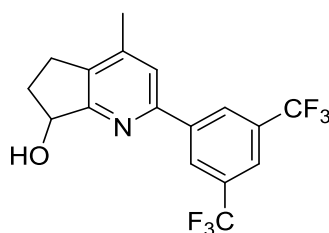
**<sup>13</sup>C{<sup>1</sup>H} NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 157.6 (s, ar-C), 154.1 (s, ar-C), 153.5 (s, ar-C), 139.1 (s, ar-C), 137.9 (s, ar-C), 134.6 (s, ar-C), 129.9 (s, ar-C), 119.2 (s, ar-C), 104 (s, ar-C), 69.1 (s, COH), 61.0 (s, OCH<sub>3</sub>), 56.3 (s, OCH<sub>3</sub>), 30.7 (s, CH<sub>2</sub>), 28.0 (s, CH<sub>2</sub>), 19.6 (s, CH<sub>2</sub>).

**IR** (KBr):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3165 (m, br), 2935 (m), 1590 (m), 1565 (m), 1511 (w), 1472 (m), 1465 (m), 1349 (m), 1237 (m), 1135 (s), 1103 (m), 965 (m), 817 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 315.1 (100), 300.1 (23), 286.2 (23), 259.1 (42), 244.1 (11).

**EA** (C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>): calc.: C 68.55, H 6.71, N 4.44; found: C 68.72, H 6.70, N 4.48.

**HPLC:** *Daicel*, Chiralpak IC (0.46 cm × 25 cm, heptane/iso-propanol = 50:50, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 23.1 min and 27.9 min

**2-(3,5-Bis(trifluoromethyl)phenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol**

The reaction was setup as described in the general procedure **GP2** except using the analogous TBS ether (430 mg, 0.90 mmol, 1.00 eq.) and TBAF  $\times$  3 H<sub>2</sub>O (1.14 g, 3.61 mmol, 4.00 eq.) dissolved in THF (5 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  15 cm, hexane:ethyl acetate (20:1  $\rightarrow$  1:1)) afforded the product (280 mg, 0.78 mmol, 86%) as a colorless solid.

C<sub>17</sub>H<sub>13</sub>F<sub>6</sub>NO (361.29 g/mol):

**MP:** 165-166 °C.

**TLC:** R<sub>f</sub> = 0.20 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 8.42 (s, 2H, ar-*H*), 7.87 (s, 1H, ar-*H*), 7.46 (s, 1H, ar-*H*), 5.27 (t,  $J_{\text{HH}}$  = 6.6 Hz, 1H, *CHOH*), 3.54 (d,  $J_{\text{HH}}$  = 2.8 Hz, 1H, *OH*), 3.03 (ddd,  $J_{\text{HH}}$  = 16.4, 8.9, 3.9 Hz, 1H, *CH*<sub>2</sub>), 2.84-2.76 (m, 1H, *CH*<sub>2</sub>), 2.63-2.58 (m, 1H, *CH*<sub>2</sub>), 2.38 (s, 3H, *CH*<sub>3</sub>), 2.13-2.04 (m, 1H, *CH*<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 165.0 (s, ar-*C*), 153.6 (s, ar-*C*), 145.4 (s, ar-*C*), 141.6 (s, ar-*C*), 136.1 (s, ar-*C*), 132.1 (q,  $J_{\text{CF}}$  = 33 Hz, ar-*C*), 127.1 (s, ar-*C*), 123.6 (q,  $J_{\text{CF}}$  = 272 Hz, CF<sub>3</sub>), 122.1 (sept,  $J_{\text{CF}}$  = 4 Hz, ar-*C*), 121.1 (s, ar-*C*), 75.0 (s, *COH*), 32.6 (s, *CH*<sub>2</sub>), 26.1 (s, *CH*<sub>2</sub>), 18.9 (s, *CH*<sub>3</sub>).

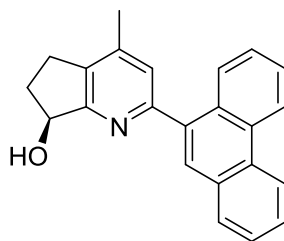
**<sup>19</sup>F{<sup>1</sup>H} NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = -63.0 (s).

**IR** (KBr):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3420 (m, br), 3073 (w), 2984 (w), 2932 (w), 1390 (m), 1334 (m), 1289 (s), 1236 (w), 1164 (m), 1127 (s), 899 (m), 684 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 361.1 (22) [M]<sup>+</sup>, 342.1 (14), 333.1 (100), 305.1 (30).

**EA** (C<sub>17</sub>H<sub>13</sub>F<sub>6</sub>NO): calc.: C 56.52, H 3.63, N 3.88; found: C 56.18, H 3.71, N 4.04.

**HPLC:** Daicel, Chiralpak AD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 220 nm): t<sub>R</sub> = 15.6 min and 18.8 min.

**(S)-4-Methyl-2-(phenanthren-9-yl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol ((S)-2.57)**

The reaction was setup as described in the general procedure **GP2** except using the analogous TBS ether (250 mg, 0.57 mmol, 1.00 eq.) and TBAF  $\times$  3 H<sub>2</sub>O (1.72 g, 2.27 mmol, 4.00 eq.) dissolved in THF (5 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  15 cm, pentane:Et<sub>2</sub>O (1:3)) afforded the product (160 mg, 0.49 mmol, 86%) as a colorless solid.

C<sub>23</sub>H<sub>19</sub>NO (325.41 g/mol):

**MP**: 232 °C (decomposition).

**TLC**: R<sub>f</sub> = 0.30 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (1:3), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 8.77 (d,  $J$  = 8.4 Hz, 1H, ar-*H*), 8.72 (d,  $J$  = 8.3 Hz, 1H, ar-*H*), 8.02 (dd,  $J$  = 8.3, 1.3 Hz, 1H, ar-*H*), 7.91 (dd,  $J$  = 7.8, 1.4 Hz, 1H, ar-*H*), 7.81 (s, 1H, ar-*H*), 7.72-7.65 (m, 2H, ar-*H*), 7.64-7.59 (m, 1H, ar-*H*), 7.58-7.52 (m, 1H, ar-*H*), 7.31 (s, 1H, ar-*H*), 5.36-5.22 (m, 1H, *H*CO), 3.12-3.00 (m, 2H, CH<sub>2</sub> and OH), 2.95-2.77 (m, 1H, CH<sub>2</sub>), 2.70-2.56 (m, 1H, CH<sub>2</sub>), 2.38 (s, 3H, CH<sub>3</sub>), 2.19-2.04 (m, 1H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 164.0 (s, ar-*C*), 158.4 (s, ar-*C*), 144.6 (s, ar-*C*), 137.4 (s, ar-*C*), 134.4 (s, ar-*C*), 131.5 (s, ar-*C*), 130.9 (s, ar-*C*), 130.7 (s, ar-*C*), 130.5 (s, ar-*C*), 129.1 (s, ar-*C*), 128.4 (s, ar-*C*), 127.1 (s, ar-*C*), 126.9 (s, ar-*C*), 126.8 (s, ar-*C*), 126.8 (s, ar-*C*), 126.7 (s, ar-*C*), 125.5 (s, ar-*C*), 123.0 (s, ar-*C*), 122.7 (s, ar-*C*), 75.4 (s, CHOH), 32.4 (s, CH<sub>2</sub>), 26.2 (s, CH<sub>2</sub>), 18.9 (s, CH<sub>3</sub>).

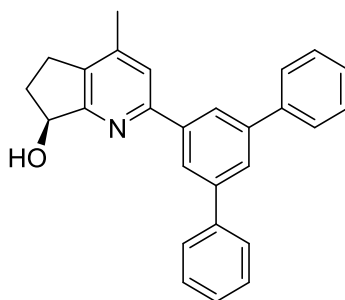
**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3353 (w), 3063 (w), 2964 (w), 1966 (w), 1592 (m), 1449 (m), 1381 (w), 1316 (w), 1261 (m), 1091 (m), 1026 (m), 954 (w), 889 (m), 801 (m), 749 (m), 710 (s).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for C<sub>23</sub>H<sub>20</sub>NO<sup>+</sup>: 326.1539 [M+H]<sup>+</sup>; found: 326.1538.

**$[\alpha]_D^{20}$**  = +0.5 ( $c$  = 1.00, CHCl<sub>3</sub>).



**(S)-2-([1,1':3',1''-Terphenyl]-5'-yl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol**  
**((S)-2.54)**



The reaction was set up as described in the general procedure **GP2** except using the analogous TBS ether (180 mg, 0.37 mmol, 1.00 eq.) and TBAF  $\times$  3 H<sub>2</sub>O (462 mg, 1.46 mmol, 4.00 eq.) dissolved in THF (7 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  15 cm, pentane:Et<sub>2</sub>O (1:3)) afforded the product (122 mg, 0.32 mmol, 88%) as a colorless solid.

C<sub>27</sub>H<sub>23</sub>NO (467.77 g/mol):

**MP:** 178-179 °C.

**TLC:** R<sub>f</sub> = 0.27 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (1:3), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 8.15 (d,  $J$  = 1.8 Hz, 2H, ar-*H*), 7.83 (t,  $J$  = 1.7 Hz, 1H, ar-*H*), 7.75-7.70 (m, 4H, ar-*H*), 7.52-7.45 (m, 5H, ar-*H*), 7.42-7.36 (m, 2H, ar-*H*), 5.26 (t,  $J$  = 6.5 Hz, 1H, *H*CO), 3.23-3.14 (m, 1H, OH), 3.05-2.94 (m, 1H, CH<sub>2</sub>), 2.84-2.71 (m, 1H, CH<sub>2</sub>), 2.62-2.54 (m, 1H, CH<sub>2</sub>), 2.35 (s, 3H, CH<sub>3</sub>), 2.14-2.01 (m, 1H, CH<sub>2</sub>).

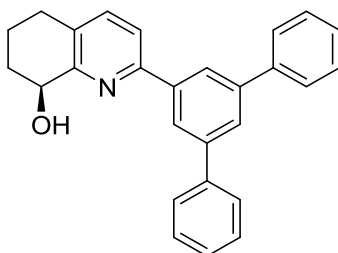
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 164.3 (s, ar-C), 156.9 (s, ar-C), 144.7 (s, ar-C), 142.4 (s, ar-C), 141.3 (s, ar-C), 140.8 (s, ar-C), 134.5 (s, ar-C), 128.9 (s, ar-C), 127.6 (s, ar-C), 127.5 (s, ar-C), 126.5 (s, ar-C), 125.1 (s, ar-C), 121.5 (s, ar-C), 75.3 (s, CHOH), 32.6 (s, CH<sub>2</sub>), 26.0 (s, CH<sub>2</sub>), 19.0 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3154 (w), 3057 (w), 2894 (w), 2844 (w), 1593 (s), 1500 (m), 1410 (m), 1312 (w), 1158 (w), 1059 (m), 1015 (m), 960 (m), 886 (m), 804 (m), 759 (s), 696 (s).

**MS** (ESI, MeOH)  $m/z$  (%): 378.5 [M+H]<sup>+</sup>.

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for C<sub>27</sub>H<sub>24</sub>NO<sup>+</sup>: 378.1852 [M+H]<sup>+</sup>; found: 378.1853.

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = +26.3 (c = 1.02, CHCl<sub>3</sub>).

**(S)-2-([1,1':3',1''-Terphenyl]-5'-yl)-5,6,7,8-tetrahydroquinolin-8-ol ((S)-2.55)**

The reaction was set up as described in the general procedure **GP2** except using the analogous TBS ether (230 mg, 0.47 mmol, 1.00 eq.) and TBAF  $\times$  3 H<sub>2</sub>O (660 mg, 1.87 mmol, 4.00 eq.) dissolved in THF (10 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  15 cm, pentane:CH<sub>2</sub>Cl<sub>2</sub> (1:3)  $\rightarrow$  CH<sub>2</sub>Cl<sub>2</sub>) afforded the product (141 mg, 0.38 mmol, 80%) as a colorless solid.

C<sub>27</sub>H<sub>23</sub>NO (377.49 g/mol):

**MP:** 141-142 °C.

**TLC:** R<sub>f</sub> = 0.49 (SiO<sub>2</sub>, pentane:CH<sub>2</sub>Cl<sub>2</sub> (1:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 8.19 (d,  $J$  = 1.8 Hz, 2H, ar-*H*), 7.85 (t,  $J$  = 1.7 Hz, 1H, ar-*H*), 7.77-7.65 (m, 5H, ar-*H*), 7.56-7.46 (m, 5H, ar-*H*), 7.45-7.38 (m, 2H, ar-*H*), 4.80-4.77 (m, 1H, CHOH), 4.38 (s, 1H, CHOH), 3.00-2.77 (m, 2H, CH<sub>2</sub>), 2.48-2.30 (m, 1H, CH<sub>2</sub>), 2.14-1.98 (m, 1H, CH<sub>2</sub>), 1.99-1.76 (m, 2H, CH<sub>2</sub>).

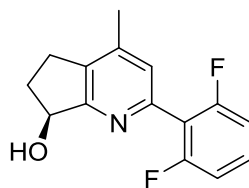
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 158.0 (s, ar-*C*), 154.3 (s, ar-*C*), 142.4 (s, ar-*C*), 141.2 (s, ar-*C*), 140.2 (s, ar-*C*), 137.9 (s, ar-*C*), 130.3 (s, ar-*C*), 129.0 (s, ar-*C*), 127.7 (s, ar-*C*), 127.5 (s, ar-*C*), 126.8 (s, ar-*C*), 124.8 (s, ar-*C*), 119.6 (s, ar-*C*), 69.3 (s, CHOH), 30.8 (s, CH<sub>2</sub>), 28.2 (s, CH<sub>2</sub>), 19.8 (s, CH<sub>2</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3036 (w), 2938 (m), 2851 (m), 1588 (m), 1567 (m), 1466 (m), 1406 (m), 1254 (m), 1073 (m), 1042 (m), 1010 (m), 961 (m), 877 (m), 827 (m), 747 (s), 690 (s), 615 (m), 589 (m), 540 (m), 499 (w), 426 (w).

**MS** (ESI, MeOH)  $m/z$  (%): 378.5 [M+H]<sup>+</sup>.

**EA** (C<sub>27</sub>H<sub>23</sub>NO): calc.: C 85.91, H 6.14, N 3.71; found: C 85.81, H 6.27, N 3.83.

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = +81.7 (c = 0.96, CHCl<sub>3</sub>).

**(S)-2-(2,6-Difluorophenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridin-7-ol ((S)-2.58)**

The reaction was set up as described in the general procedure **GP2** except using the analogous TBS ether (250 mg, 0.67 mmol, 1.00 eq.) and TBAF  $\times$  3 H<sub>2</sub>O (840 mg, 2.66 mmol, 4.00 eq.) dissolved in THF (12 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  10 cm, pentane:Et<sub>2</sub>O (1:3)) afforded the product (172 mg, 0.66 mmol, 99%) as a colorless solid.

C<sub>15</sub>H<sub>13</sub>F<sub>2</sub>NO (261.27 g/mol):

**MP:** 126-127 °C.

**TLC:** R<sub>f</sub> = 0.20 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (1:3), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.31 (tt, *J* = 8.4, 6.3 Hz, 1H, ar-*H*), 7.13 (s, 1H, ar-*H*), 7.01-6.92 (m, 2H, ar-*H*), 5.27-5.21 (m, 1H, *H*CO), 3.77-3.62 (m, 1H, OH), 3.05-2.91 (m, 1H, CH<sub>2</sub>), 2.82-2.68 (m, 1H, CH<sub>2</sub>), 2.59-2.44 (m, 1H, CH<sub>2</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 2.10-1.97 (m, 1H, CH<sub>2</sub>).

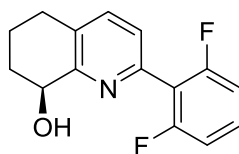
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 164.5 (s, ar-C), 160.6 (dd, *J*<sub>CF</sub> = 250, 7 Hz, ar-C), 147.8 (s, ar-C), 144.4 (s, ar-C), 135.4 (s, ar-C), 129.9 (t, *J*<sub>CF</sub> = 10 Hz, ar-C), 126.0 (s, ar-C), 118.2 (t, *J*<sub>CF</sub> = 19 Hz, ar-C), 113.2-109.9 (m, ar-C), 74.8 (d, *J*<sub>CF</sub> = 13 Hz, CHOH), 32.4 (d, *J*<sub>CF</sub> = 7 Hz, CH<sub>2</sub>), 26.1 (s, CH<sub>2</sub>), 18.7 (s, CH<sub>3</sub>).

**<sup>19</sup>F{<sup>1</sup>H} NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = -114.1.

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3295 (w), 2962 (w), 2854 (w), 2451 (w), 1599 (m), 1467 (s), 1372 (w), 1312 (w), 1272 (m), 1233 (m), 1167 (w), 1087 (s), 1001 (s), 954 (m), 926 (m), 877 (m), 860 (w), 791 (s), 735 (s), 644 (m).

**HRMS** (ESI, 4500 V, 180 °C): (*m/z*) calc. for C<sub>15</sub>H<sub>14</sub>F<sub>2</sub>NO<sup>+</sup>: 262.1038 [M+H]<sup>+</sup>; found: 262.1040.

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = +4.1 (c = 0.98, CHCl<sub>3</sub>).

**(S)-2-(2,6-Difluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol ((S)-2.59)**

The reaction was set up as described in the general procedure **GP2** except using the analogous TBS ether (580 mg, 1.57 mmol, 1.00 eq.) and TBAF  $\times$  3 H<sub>2</sub>O (3.24 g, 10.3 mmol, 4.00 eq.) dissolved in THF (25 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  15 cm, pentane:Et<sub>2</sub>O (1:3)) afforded the product (324 mg, 1.25 mmol, 85%) as a colorless solid.

C<sub>15</sub>H<sub>13</sub>NO (261.27 g/mol):

**MP:** 94-96 °C.

**TLC:** R<sub>f</sub> = 0.35 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (1:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.43 (d,  $J$  = 7.9 Hz, 1H, ar-*H*), 7.33-7.22 (m, 2H, ar-2*H*), 6.97-6.82 (m, 2H, ar-*H*), 4.67 (t,  $J$  = 5.9 Hz, 1H, *CHOH*), 3.97 (s, 1H, *CHOH*), 2.87-2.69 (m, 2H, CH<sub>2</sub>), 2.31-2.19 (m, 1H, CH<sub>2</sub>), 2.02-1.90 (m, 1H, CH<sub>2</sub>), 1.84-1.69 (m, 2H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 160.7 (dd,  $^1J$  = 250 Hz,  $^3J$  = 7 Hz, ar-*qC*), 158.2 (s, ar-*qC*), 146.5 (s, ar-*qC*), 137.2 (s, ar-*CH*), 131.1 (s, ar-*qC*), 130.0 (t,  $^3J$  = 10 Hz, ar-*qC*), 124.6 (t,  $^3J$  = 2 Hz, ar-*C*), 117.9 (t,  $^2J$  = 18 Hz, ar-*qC*), 111.9 (dd,  $J$  = 18, 8 Hz, ar-*C*), 69.1 (s, *CHOH*), 30.7 (s, CH<sub>2</sub>), 28.3 (s, CH<sub>2</sub>), 19.6 (s, CH<sub>2</sub>).

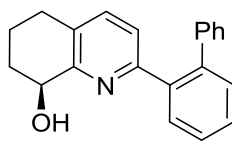
**<sup>19</sup>F{<sup>1</sup>H} NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = -114.4 (s).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3258 (br m), 2942 (m), 2860 (m), 1624 (w), 1467 (s), 1232 (m), 998 (s), 924 (m), 830 (s), 776 (s).

**MS** (ESI, MeOH ( $m/z$ ): 284.1 (80) [M+Na]<sup>+</sup>, 545.3 (100) [2M+Na]<sup>+</sup>.

**EA** (C<sub>15</sub>H<sub>13</sub>NOF<sub>2</sub>): calc.: C 68.96, H 5.02, N 5.36; found: C 68.60, H 5.10, N 5.55.

**$[\alpha]_D^{20}$**  = +74.1 (c = 0.58, CHCl<sub>3</sub>).

**(S)-2-([1,1'-Biphenyl]-2-yl)-5,6,7,8-tetrahydroquinolin-8-ol ((S)-2.56)**

The reaction was set up as described in the general procedure **GP2** except using the analogous TBS ether (217 mg, 0.523 mmol, 1.00 eq.) and TBAF  $\times$  3 H<sub>2</sub>O (0.634 mg, 2.18 mmol, 4.00 eq.) dissolved in THF (8 mL). Extraction and purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  10 cm, pentane:Et<sub>2</sub>O (1:1)) afforded the product (122 mg, 0.405 mmol, 77%) as a colorless solid.

C<sub>21</sub>H<sub>19</sub>NO (301.17 g/mol)

**MP:** 46-49 °C.

**TLC:** R<sub>f</sub> = 0.38 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (1:1), UV).

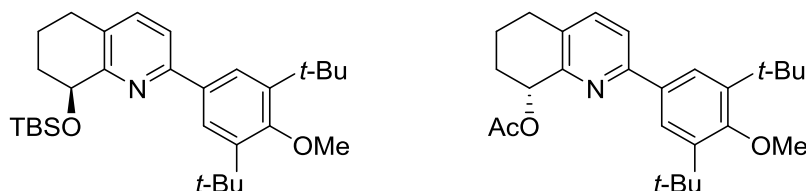
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.64-7.58 (m, 1H, ar-*H*), 7.42-7.33 (m, 3H, ar-*H*), 7.24-7.17 (m, 3H, ar-*H*), 7.15 (d, *J* = 7.9 Hz, 1H, ar-*H*), 7.11-7.06 (m, 2H, ar-*H*), 6.87 (d, *J* = 7.9 Hz, 1H, ar-*H*), 4.50 (t, *J* = 7.8 Hz, 1H, OCH), 3.40 (s, 1H, COH), 2.80-2.58 (m, 2H, CH<sub>2</sub>), 2.26-2.10 (m, 1H, CH<sub>2</sub>), 1.95-1.81 (m, 1H, CH<sub>2</sub>), 1.79-1.59 (m, 2H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 157.2 (s, ar-C), 156.1 (s, ar-C), 141.9 (s, ar-C), 141.0 (s, ar-C), 138.9 (s, ar-C), 136.6 (s, ar-C), 130.8 (s, ar-C), 130.3 (s, ar-C), 129.5 (s, ar-C), 129.1 (s, ar-C), 128.5 (s, ar-C), 128.1 (s, ar-C), 127.6 (s, ar-C), 126.6 (s, ar-C), 123.4 (s, ar-C), 68.8 (s, CHOH), 30.6 (s, CH<sub>2</sub>), 28.0 (s, CH<sub>2</sub>), 19.5 (s, CH<sub>2</sub>).

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = +45.4 (c = 0.50, CHCl<sub>3</sub>).

## General procedure: Kinetic enzymatic resolutions GP3

**(*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline ((*S*)-2.41) and (*R*)-2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-8-yl acetate**



Vinyl acetate (1.30 mL, 21.1 mmol, 15.0 eq.) and CAL-B [250 mg, immobilized on acrylic resin from Sigma (L47777)] was added to a solution of the racemic alcohol **2.51** (514 mg, 1.40 mmol, 1.00 eq.) in dry *i*-Pr<sub>2</sub>O (60 mL). The resulting solution was stirred at 60 °C for 5.5 h until chiral HPLC showed full consumption of one enantiomer. The enzyme was filtered off and washed with EtOAc (3 × 20 mL). Evaporation of the solvent afforded a pale yellow residue which was dissolved in DMF (5 mL). Imidazole (160 mg, 2.35 mmol, 1.70 eq.) and TBSCl (170 mg, 1.12 mmol, 0.80 eq.) were added under an argon atmosphere. The resulting colorless solution was stirred for 18 h at room temperature. The solvent was evaporated in HV and the resulting pale yellow residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and H<sub>2</sub>O (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under reduced pressure to afford a colorless residue. Column chromatography (SiO<sub>2</sub>, d × h: 6 × 30 cm, hexane:ethyl acetate (1:20 → 1:1)) afforded the TBS ether (*S*)-**2.41** (310 mg, 0.64 mmol, 46%) as a colorless solid and the (*R*)-acetate (250 mg, 0.61 mmol, 44%) as a colorless oil.

### TBS ether (*S*)-2.41

C<sub>24</sub>H<sub>35</sub>NO<sub>4</sub>Si (429.63 g/mol):

[α]<sub>D</sub><sup>20</sup> = +30.8 (c = 0.73, CHCl<sub>3</sub>).

Additional analytical data matches the data of the racemic silyl ether **2.41**.

### (*R*)-Acetate

C<sub>26</sub>H<sub>35</sub>NO<sub>3</sub> (409.57 g/mol):

TLC: R<sub>f</sub> = 0.64 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.86 (s, 2H, ar-*H*), 7.53 (d,  $J_{\text{HH}}$  = 8.0 Hz, 1H, ar-*H*), 7.45 (d,  $J_{\text{HH}}$  = 8.0 Hz, 1H, ar-*H*), 6.08 (t,  $J_{\text{HH}}$  = 5.7 Hz, 1H, *HCOAc*), 3.71 (s, 3H, *OCH*<sub>3</sub>), 2.87 (dt,  $J_{\text{HH}}$  = 16.7, 6.2 Hz, 1H, *CH*<sub>2</sub>), 2.77 (dt,  $J_{\text{HH}}$  = 16.7, 6.2 Hz, 1H, *CH*<sub>2</sub>), 2.17-2.10 (m, 2H, *CH*<sub>2</sub>), 2.15 (s, 3H, *CH*<sub>3</sub>), 2.03-1.95 (m, 1H, *CH*<sub>2</sub>), 1.91-1.83 (m, 1H, *CH*<sub>2</sub>), 1.47 (s, 18H, 2  $\times$  *C(CH*<sub>3</sub>)<sub>3</sub>).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ): 170.8 (s, *O*<sub>2</sub>*CCH*<sub>3</sub>), 160.7 (s, ar-*C*), 155.9 (s, ar-*C*), 153.3 (s, ar-*C*), 143.9 (s, ar-*C*), 137.6 (s, ar-*C*), 133.6 (s, ar-*C*), 130.9 (s, ar-*C*), 125.4 (s, ar-*C*), 119.5 (s, ar-*C*), 71.2 (s, *COAc*) 64.4 (*OCH*<sub>3</sub>), 36.1 (s, *C(CH*<sub>3</sub>)<sub>3</sub>), 32.2 (s, *C(CH*<sub>3</sub>)<sub>3</sub>), 29.3 (s, *CH*<sub>2</sub>), 28.2 (s, *CH*<sub>2</sub>), 21.6 (s, *CH*<sub>3</sub>), 19.4 (s, *CH*<sub>2</sub>).

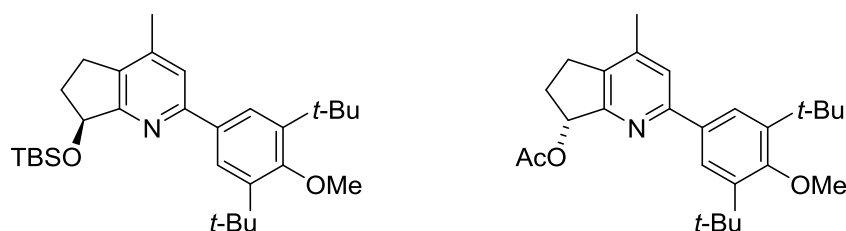
**IR** (NaCl):  $\tilde{\nu}/\text{cm}^{-1}$  = 2956 (s), 1739 (s), 1593 (w), 1559 (w), 1412 (m), 1369 (w), 1236 (s), 1115 (w), 1012 (m), 756 (w).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 410.3 (17), 409.3 (59), 367.3 (14), 366.3 (49), 350.3 (12), 349.3 (29), 335.3 (24), 334.3 (100), 304.2 (11).

**HPLC**: *Daicel*, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 99.5:0.5, 0.5 mL/min, 25 °C, 220 nm): *t*<sub>R</sub> = 26.4 min and 32.1 min.

$[\alpha]_{\text{D}}^{20}$  = +19.6 (*c* = 0.53,  $\text{CHCl}_3$ ).

**(*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine ((*S*)-2.38) and (*R*)-2-(3,5-di-*tert*-Butyl-4-methoxyphenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[*b*]pyridin-7-yl acetate**



The reaction was set up as described in the general procedure **GP3** except using vinyl acetate (2.00 mL, 32.5 mmol, 32.5 eq.), CAL-B (200 mg) and the analogous racemic alcohol (370 mg, 1.00 mmol, 1.00 eq.) in dry *i*-Pr<sub>2</sub>O (80 mL) stirred at 60 °C for 4.5 h. After workup the mixture was dissolved in DMF (8 mL). Imidazole (115 mg, 1.69 mmol, 1.70 eq.) and TBSCl (125 mg, 0.82 mmol, 0.80 eq.) were added to the solution under an argon atmosphere and the reaction was stirred for 18 h. Evaporation of the solvent, extraction and column chromatography (SiO<sub>2</sub>, d  $\times$  h: 6  $\times$  30 cm, hexane:ethyl acetate (1:20  $\rightarrow$  1:3)) afforded the TBS

ether (*S*)-**2.38** (240 mg, 0.49 mmol, 49%) as a colorless solid and the (*R*)-acetate (200 mg, 0.48 mmol, 48%) as a colorless oil.

**TBS ether (*S*)-2.38**

C<sub>24</sub>H<sub>35</sub>NO<sub>4</sub>Si (429.63 g/mol):

$[\alpha]_D^{20} = +12.1$  (c = 0.94, CHCl<sub>3</sub>).

Additional analytical data matches the data of the racemic silyl ether (*S*)-**2.38**

**(*R*)-Acetate**

C<sub>26</sub>H<sub>35</sub>NO<sub>3</sub> (409.57 g/mol):

**TLC:** R<sub>f</sub> = 0.26 (SiO<sub>2</sub>, hexane:ethyl acetate (5:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.78 (s, 2H, ar-*H*), 7.35 (s, 1H, ar-*H*), 6.17 (dd, *J*<sub>HH</sub> = 7.3, 4.4 Hz, 1H, HCOAc), 3.71 (s, 3H, OCH<sub>3</sub>), 3.02 (ddd, *J*<sub>HH</sub> = 16.1, 8.8, 5.4 Hz, 1H, CH<sub>2</sub>), 3.83 (ddd, *J*<sub>HH</sub> = 16.0, 8.6, 5.3 Hz, 1H, CH<sub>2</sub>), 2.68-2.59 (m, 1H, CH<sub>2</sub>), 2.35 (s, 3H, CH<sub>3</sub>), 2.16-2.08 (m, 1H CH<sub>2</sub>), 2.13 (s, 3H, O<sub>2</sub>CCH<sub>3</sub>), 1.48 (s, 18H, 2 × C(CH<sub>3</sub>)<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 171.1 (s, O<sub>2</sub>CCH<sub>3</sub>), 160.6 (s, ar-C), 160.0 (s, ar-C), 158.5 (s, ar-C), 144.3 (s, ar-C), 143.8 (s, ar-C), 134.9 (s, ar-C), 134.3 (s, ar-C), 125.8 (s, ar-C), 121.7 (s, ar-C), 77.9 (s, COAc), 64.5 (s, OCH<sub>3</sub>), 36.0 (s, C(CH<sub>3</sub>)<sub>3</sub>), 32.2 (s, C(CH<sub>3</sub>)<sub>3</sub>), 30.7 (s, CH<sub>2</sub>), 26.4 (s, CH<sub>2</sub>), 21.5 (s, CH<sub>3</sub>), 19.0 (s, CH<sub>3</sub>).

**IR** (NaCl):  $\tilde{\nu}/\text{cm}^{-1}$  = 2965 (m), 1734 (s), 1597 (w), 1444 (w), 1405 (m), 1363 (m), 1242 (s), 1219 (s), 1115 (w), 1003 (m), 889 (w).

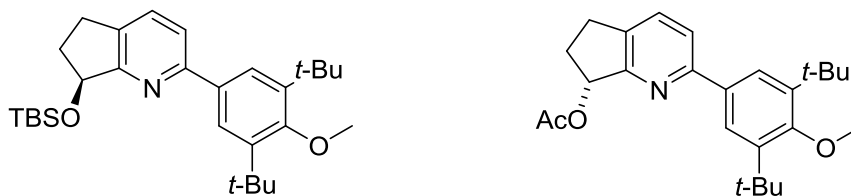
**MS** (EI, 70 eV, 200 °C) *m/z* (%): 410.3 (15), 409.3 (51), 366.3 (19), 350.3 (17), 349.2 (45), 348.3 (12), 335.3 (26), 334.2 (100), 304.2 (25), 292.2 (16), 278.2 (11).

$[\alpha]_D^{20} = -29.2$  (c = 0.84, CHCl<sub>3</sub>).

**HPLC:** Daicel, Chiralpak IC (0.46 cm × 25 cm, heptane/iso-propanol = 50:50, 0.5 mL/min, 25 °C, 220 nm): t<sub>R</sub> = 22.5 min and 23.5 min.



**(S)-7-((*tert*-Butyldimethylsilyl)oxy)-2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta-[b]pyridine and (R)-2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate**



The reaction was set up as described in the general procedure **GP3** except using vinyl acetate (7.80 mL, 84.3 mmol, 45.8 eq.), CAL-B (46.8 mg) and 2-(3,5-di-*tert*-butyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (650 mg, 1.84 mmol, 1.00 eq.) in dry *i*-Pr<sub>2</sub>O (65 mL) stirred for 3 h at 60 °C. After workup the mixture was dissolved in DMF (5 mL). Imidazole (202 mg, 2.97 mmol, 1.70 eq.) and TBSCl (220 mg, 1.44 mmol, 0.80 eq.) were added to the solution under an argon atmosphere and the reaction was stirred for 18 h. Evaporation of the solvent, extraction and column chromatography (SiO<sub>2</sub>, d × h: 6 × 30 cm, pentane:Et<sub>2</sub>O (40:1 → 1:1)) afforded the (*S*)-TBS ether (386 mg, 830 μmol, 45%, >99.9% *ee*) as a colorless solid and the (*R*)-acetate (371 mg, 938 μmol, 45%, 82% *ee*) as pale yellow solid.

C<sub>29</sub>H<sub>45</sub>NO<sub>2</sub>Si (467.77 g/mol):

**TLC:** R<sub>f</sub> = 0.50 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (40:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.97 (s, 2H, ar-*H*), 7.54 (s, 2H, ar-*H*), 5.26-5.32 (m, 1H, HCOSi), 3.73 (s, 3H, OCH<sub>3</sub>), 3.09-3.02 (m, 1H, CH<sub>2</sub>), 2.82-2.75 (m, 1H, CH<sub>2</sub>), 2.51-2.42 (m, 1H, CH<sub>2</sub>), 2.10-2.07 (m, 1H, CH<sub>2</sub>), 1.50 (s, 18H, 2 × C(CH<sub>3</sub>)<sub>3</sub>), 1.00 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.31 and 0.24 (s, 6H, SiCH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 163.3 (s, ar-*C*), 159.3 (s, ar-*C*), 155.6 (s, ar-*C*), 142.6 (s, ar-*C*), 132.9 (s, ar-*C*), 132.8 (s, ar-*C*), 132.1 (s, ar-*C*), 124.3 (s, ar-*C*), 117.9 (s, ar-*C*), 75.2 (s, CHOSi), 63.2 (s, OCH<sub>3</sub>), 34.9 (s, 2 × C(CH<sub>3</sub>)<sub>3</sub>), 33.3 (s, CH<sub>2</sub>), 31.1 (s, 2 × C(CH<sub>3</sub>)<sub>3</sub>), 26.1 (s, CH<sub>2</sub>), 25.0 (s, SiC(CH<sub>3</sub>)<sub>3</sub>), 17.6 (s, SiC(CH<sub>3</sub>)<sub>3</sub>), -5.1 and -5.6 (s, Si(CH<sub>3</sub>)<sub>2</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2955 (m), 2854 (m), 1591 (w), 1444 (m), 1411 (m), 1389 (m), 1360 (m), 1318 (w), 1244 (m), 1220 (m), 1156 (w), 1104 (m), 1079 (m), 860 (m), 826 (s), 780 (s), 679 (w), 616 (w).

**HRMS** (ESI, 4500 V, 180 °C): (*m/z*) calc. for C<sub>29</sub>H<sub>46</sub>NO<sub>2</sub>Si<sup>+</sup>: 468.3292 [M+H]<sup>+</sup>; found: 468.3297.

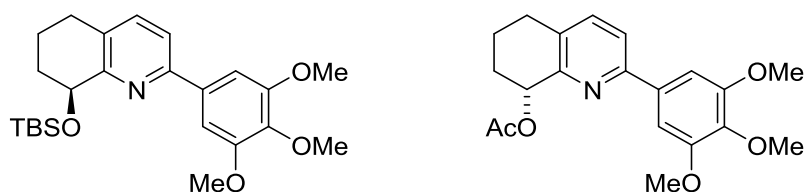
[ $\alpha$ ]<sub>D</sub><sup>20</sup> = +24.6 (c = 0.98, CHCl<sub>3</sub>).

$C_{25}H_{33}NO_3$  (395.54 g/mol):

$[\alpha]_D^{20} = -14.6$  ( $c = 0.54$ ,  $CHCl_3$ ).

Additional analytical data matches the data of the racemic acetate.

**(S)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydroquinoline ((S)-2.42) and (R)-2-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydroquinolin-8-yl acetate**



The reaction was setup as described in the general procedure **GP3** except using vinyl acetate (0.28 mL, 4.55 mmol, 7.50 eq.), CAL-B (500 mg) and the racemic alcohol **2.53** (183 mg, 0.61 mmol, 1.00 eq.) in dry *i*-Pr<sub>2</sub>O (100 mL) stirred at 60 °C for 7 h. After workup the mixture was dissolved in DMF (5 mL). Imidazole (800 mg, 1.17 mmol, 1.90 eq.) and TBSCl (800 mg, 0.52 mmol, 0.80 eq.) were added. Evaporation of the solvent, extraction and column chromatography (SiO<sub>2</sub>, d × h: 6 × 30 cm, hexane:ethyl acetate (1:20 → 3:1)) afforded the TBS ether **(S)-2.42** (120 mg, 2.77 mmol, 45%) as a colorless solid and the (*R*)-acetate (100 mg, 0.28 mmol, 46%) as a colorless oil.

#### (R)-Acetate

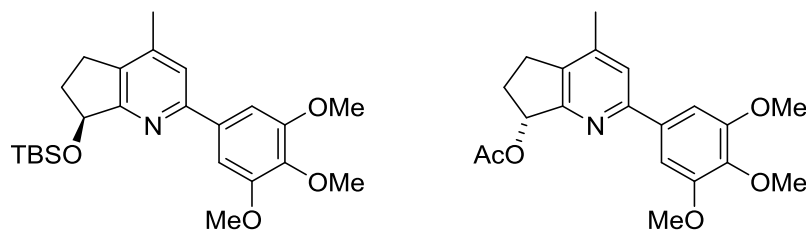
$C_{20}H_{23}NO_5$  (357.41 g/mol):

**TLC:**  $R_f = 0.56$  (SiO<sub>2</sub>, hexane:ethyl acetate (1:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.56 (d,  $J_{HH} = 8.1$  Hz, 1H, ar-*H*), 7.48 (d,  $J_{HH} = 8.1$  Hz, 1H, ar-*H*), 7.25 (s, 2H, ar-*H*), 6.04 (t,  $J_{HH} = 5.4$  Hz, 1H, HCOAc), 3.94 (s, 6H, 2 × OCH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 2.85 (dt,  $J_{HH} = 16.9, 5.8$  Hz, 1H, CH<sub>2</sub>), 2.78-2.71 (m, 1H, CH<sub>2</sub>), 2.16-2.07 (m, 2H, CH<sub>2</sub>), 2.14 (s, 3H, CH<sub>3</sub>), 2.05-1.95 (m, 1H, CH<sub>2</sub>), 1.91-1.84 (m, 1H, CH<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 170.7 (s, O<sub>2</sub>CCH<sub>3</sub>), 154.6 (s, ar-C), 153.5 (s, ar-C), 153.2 (s, ar-C), 139.1 (s, ar-C), 138.0 (s, ar-C), 134.7 (s, ar-C), 131.7 (s, ar-C), 119.5 (s, ar-C), 104.1 (s, ar-C), 71.1 (s, HCOAc), 61.1 (s, OCH<sub>3</sub>), 56.3 (s, OCH<sub>3</sub>), 29.1 (s, CH<sub>2</sub>), 28.2 (s, CH<sub>2</sub>), 21.6 (s, CH<sub>3</sub>), 19.0 (s, CH<sub>2</sub>).

**(*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-2-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-cyclopenta[*b*]pyridine ((*S*)-2.39) and (*R*)-4-methyl-2-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-cyclopenta[*b*]pyridin-7-yl acetate**



The reaction was set up as described in the general procedure **GP3** except using vinyl acetate (1.20 mL, 19.48 mmol, 15.0 eq.), CAL-B (100 mg) and the analogous racemic alcohol **2.52** (390 mg, 1.30 mmol, 1.00 eq.) in *i*-Pr<sub>2</sub>O (180 mL) stirred at 60 °C for 5.5 h. After work up the mixture was dissolved in DMF (5 mL). Imidazole (120 mg, 1.75 mmol, 1.50 eq.) and TBSCl (150 mg, 0.98 mmol, 0.80 eq.) were added under an argon atmosphere and the reaction was stirred for 18 h. Evaporation of the solvent, extraction and column chromatography (SiO<sub>2</sub>, d × h: 6 × 30 cm, hexane:ethyl acetate (5:1 → 1:3)) afforded the TBS ether (*S*)-**2.39** (118 mg, 0.27 mmol, 21%) and the (*R*)-acetate (167 mg, 0.47 mmol, 36%) both as a colorless solids.

#### TBS ether (*S*)-2.39

C<sub>24</sub>H<sub>35</sub>NO<sub>4</sub>Si (429.63 g/mol):

[α]<sub>D</sub><sup>20</sup> = +16.9 (c = 0.65, CHCl<sub>3</sub>).

Additional analytical data matches the data of the racemic silyl ether **2.39**.

#### (*R*)-Acetate

C<sub>20</sub>H<sub>23</sub>NO<sub>5</sub> (357.41 g/mol):

**MP:** 130-133 °C.

**TLC:** R<sub>f</sub> = 0.40 (SiO<sub>2</sub>, hexane:ethyl acetate (1:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.39 (s, 1H, ar-*H*), 7.18 (s, 2H, ar-*H*), 6.15 (dd, *J*<sub>HH</sub> = 7.1, 4.0 Hz, 1H, *H*COAc), 3.95 (s, 6H, 2 × OCH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 3.06-2.98 (m, 1H, CH<sub>2</sub>), 2.83 (ddd, *J*<sub>HH</sub> = 16.0, 8.6, 4.7 Hz, 1H, CH<sub>2</sub>), 2.67-2.58 (m, 1H, CH<sub>2</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 2.16-2.08 (m, 1H, CH<sub>2</sub>), 2.12 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 171.0 (s, O<sub>2</sub>CCH<sub>3</sub>), 160.0 (s, ar-C), 157.2 (s, ar-C), 153.3 (s, ar-C), 144.7 (s, ar-C), 139.0 (s, ar-C), 135.8 (s, ar-C), 135.4 (s, ar-C), 121.6 (s, ar-C), 104.5 (s, ar-C), 77.8 (s, COAc), 61.0 (s, OCH<sub>3</sub>), 56.4 (s, OCH<sub>3</sub>), 30.7 (s, CH<sub>2</sub>), 26.4 (s, CH<sub>2</sub>), 21.5 (s, O<sub>2</sub>CCH<sub>3</sub>), 19.0 (s, CH<sub>3</sub>).

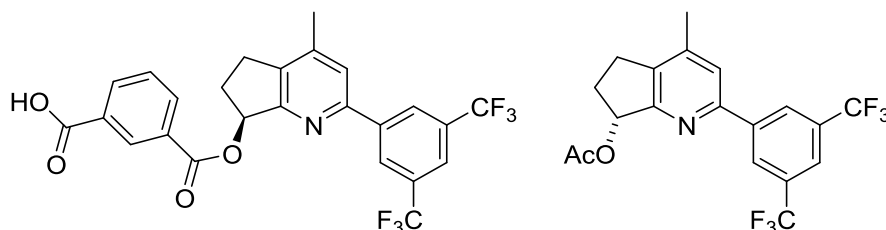
**MS** (EI, 70 eV, 250 °C)  $m/z$  (%): 358.2 (21), 357.1 (100), 314.1 (35), 298.1 (16), 297.1 (35), 296.1 (30), 283.1 (10), 282.1 (56), 266.1 (10), 254.1 (11), 251.1 (12), 224.1 (14).

**IR** (NaCl):  $\tilde{\nu}/\text{cm}^{-1}$  = 3012 (w), 2951 (m), 2827 (w), 1723 (s), 1586 (m), 1509 (m), 1264 (m), 1413 (m), 1363 (m), 1232 (s), 1130 (s), 1024 (m), 1004 (m), 959 (m), 846 (m), 771 (w).

$[\alpha]_D^{20} = -42.1$  ( $c = 0.43$ ,  $\text{CHCl}_3$ ).

**HPLC**: *Daicel*, Chiralpak AD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 80:20, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 17.6 min and 19.3 min.

**(S)-3-(((2-(3,5-Bis(trifluoromethyl)phenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)oxy)carbonyl)benzoic acid and (R)-2-(3,5-Bis(trifluoromethyl)phenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl acetate**



Vinyl acetate (0.5 mL, 8.12 mmol, 14.8 eq.) and CAL-B [107 mg, immobilized on acrylic resin from Sigma (L47777)] was added to a solution of the analogous racemic alcohol (200 mg, 0.55 mmol, 1.00 eq.) in *i*-Pr<sub>2</sub>O (27 mL). The resulting solution was stirred at 60 °C for 5.5 h until HPLC showed full consumption of one enantiomer. The enzyme was filtered off and washed with EtOAc (3  $\times$  20 mL). Evaporation of the solvent afforded a pale yellow residue. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL). Phthalic anhydride (53 mg, 0.35 mmol, 0.60 eq.), and Et<sub>3</sub>N (54  $\mu$ L) were added. The solution was heated to reflux for 6 h. The mixture was washed with sat. NH<sub>4</sub>Cl solution (2  $\times$  20 mL) and the organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated on a rotovap. Purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  30 cm, hexane:CH<sub>2</sub>Cl<sub>2</sub>:methanol (10:1:0  $\rightarrow$  0:10:1)) afforded the (*S*)-benzoic acid (133 mg, 0.26 mmol, 46%) and the (*R*)-acetate (103 mg, 0.26 mmol, 46%) both as a colorless solids.

#### (S)-Carboxylic acid

C<sub>25</sub>H<sub>17</sub>F<sub>6</sub>NO<sub>5</sub> (509.40 g/mol):

**TLC**:  $R_f$  = 0.48 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:MeOH (20:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ): 8.46 (s, 2H, ar-*H*), 7.88 (s, 1H, ar-*H*), 7.79 (s, 2H, ar-*H*), 7.58-7.43 (m, 3H, ar-*H*), 6.47-6.40 (m, 1H, *HCO*), 3.12-2.97 (m, 2H,  $\text{CH}_2$ ), 2.92-2.69 (m, 2H,  $\text{CH}_2$ ), 2.36 (s, 3H,  $\text{CH}_3$ ), 2.29-2.22 (m, 1H,  $\text{CH}_2$ ).

**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = -63.0$  (s).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 2920$  (m), 2850 (m), 1727 (m), 1702 (m), 1596 (m), 1558 (m), 1449 (m), 1391 (m), 1320 (m), 1275 (s), 1175 (m), 1122 (s), 1074 (m), 1029 (w), 933 (w), 896 (m), 745 (m), 710 (m), 680 (m).

**MS** (EI, 70 eV, 250 °C)  $m/z$  (%): 510.0 (21), 344.3 (100).

#### (*R*)-Acetate

$\text{C}_{19}\text{H}_{15}\text{F}_6\text{NO}_2$  (403.32 g/mol):

**TLC**:  $R_f = 0.60$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 8.44$  (s, 2H, ar-*H*), 7.88 (s, 1H, ar-*H*), 7.52 (s, 1H, ar-*H*), 6.17 (dd,  $J_{\text{HH}} = 7.2$  Hz,  $J_{\text{HH}} = 4.4$  Hz, 1H, *HCOAc*), 3.06 (ddd,  $J_{\text{HH}} = 16.1$  Hz,  $J_{\text{HH}} = 8.8$  Hz,  $J_{\text{HH}} = 5.4$  Hz, 1H,  $\text{CH}_2$ ), 2.88 (ddd,  $J_{\text{HH}} = 16.6$  Hz,  $J_{\text{HH}} = 8.6$  Hz,  $J_{\text{HH}} = 5.3$  Hz, 1H,  $\text{CH}_2$ ), 2.73-2.64 (m, 1H,  $\text{CH}_2$ ), 2.40 (s, 3H,  $\text{CH}_3$ ), 2.19-2.11 (m, 1H,  $\text{CH}_2$ ), 2.16 (s, 3H,  $\text{O}_2\text{CCH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 170.9$  (s,  $\text{O}_2\text{CCH}_3$ ), 160.9 (s, ar-*C*), 154.04 (s, ar-*C*), 145.5 (s, ar-*C*), 141.4 (s, ar-*C*), 137.5 (s, ar-*C*), 132.1 (q,  $J_{\text{CF}} = 33$  Hz, ar-*C*), 127.2 (s, ar-*C*), 123.8 (q,  $J_{\text{CF}} = 271$  Hz,  $\text{CF}_3$ ), 122.4-122.2 (m, ar-*C*), 121.9 (s, ar-*C*), 77.4 (s, *COAc*), 30.7 (s,  $\text{CH}_2$ ), 26.5 (s,  $\text{CH}_2$ ), 21.5 (s,  $\text{CH}_3$ ), 19.1 (s,  $\text{CH}_3$ ).

**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = -63.0$  (s).

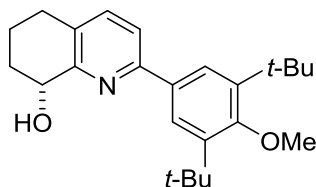
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 2961$  (w), 2920 (w), 2850 (w), 1717 (s), 1596 (m), 1446 (w), 1391 (m), 1380 (m), 1284 (s), 1254 (m), 1241 (m), 1164 (m), 1121 (s), 1087 (m), 1024 (m), 951 (m), 896 (m), 796 (m), 697 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 403.1 (3), 360.0 (99), 343.0 (100).

**HPLC**: *Daicel*, Chiralpak AD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 220 nm):  $t_R = 12.9$  min and 17.3 min.

## General procedure: Saponifications of carboxylic acid esters GP4

### (*R*)-2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-8-ol



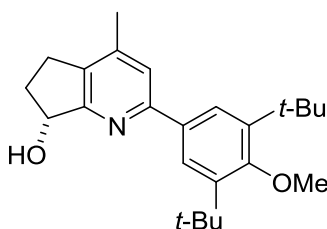
The analogous acetate (250 mg, 0.61 mmol, 1.00 eq.) was dissolved in a mixture of MeOH:THF ((1:1), 4 mL) and 2 M NaOH (2 mL) was added. The pale yellow solution was stirred for 16 h at room temperature. The solvent was evaporated under reduced pressure and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and H<sub>2</sub>O (30 mL) were added. The organic layers was separated and washed with H<sub>2</sub>O (2 × 30 mL). The organic layer was dried over MgSO<sub>4</sub> and filtered. Evaporation of the solvent and drying in HV afforded the product (212 mg, 0.57 mmol, 95%, 99.1% *ee*) as a colorless solid.

C<sub>24</sub>H<sub>33</sub>NO<sub>2</sub> (357.41 g/mol):

$[\alpha]_D^{20} = -97.6$  ( $c = 0.82$ , CHCl<sub>3</sub>).

Additional analytical data match the racemic alcohol.

### (*R*)-2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol



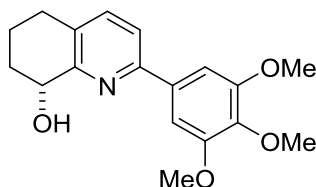
The reaction was set up as described in the general procedure **GP4** except using the analogous (*R*)-acetate (200 mg, 0.48 mmol, 1.00 eq.) in a mixture of MeOH:THF ((1:1), 4 mL) and 2 M NaOH (1.8 mL). Extraction and drying in HV afforded the alcohol (*R*)-**2.50** (175 mg, 0.48 mmol, 98%, 98.6% *ee*) as a colorless solid. Recrystallization from hexane (8.5 mL), filtration of the scalemic crystals and evaporation of the solvent afforded the product (167 mg, 0.46 mmol, 95%) in enriched enantioselectivity (99.2% *ee*) as a colorless solid.

C<sub>24</sub>H<sub>33</sub>NO<sub>2</sub> (357.41 g/mol):

$[\alpha]_D^{20} = -14.9$  ( $c = 0.75$ ,  $\text{CHCl}_3$ ).

Additional analytical data match the racemic alcohol.

**(R)-2-(3,4,5-Trimethoxyphenyl)-5,6,7,8-tetrahydroquinolin-8-ol**



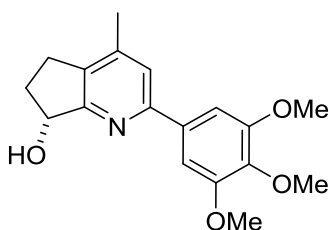
The reaction was set up as described in the general procedure **GP4** except using the analogous (*R*)-acetate (90.0 mg, 0.25 mmol, 1.00 eq.) in a mixture of MeOH (2 mL) and 2 M NaOH (0.9 mL). Extraction and purification by column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 30$  cm, hexane:ethyl acetate (10:1  $\rightarrow$  1:2)) afforded the product (56.0 mg, 0.18 mmol, 71%, 97.2% *ee*) as a colorless solid.

$\text{C}_{18}\text{H}_{21}\text{NO}_4$  (357.41 g/mol):

$[\alpha]_D^{20} = -104.7$  ( $c = 0.56$ ,  $\text{CHCl}_3$ ).

Additional analytical data match the racemic alcohol **2.51**.

**(R)-4-Methyl-2-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol ((R)-2.52)**

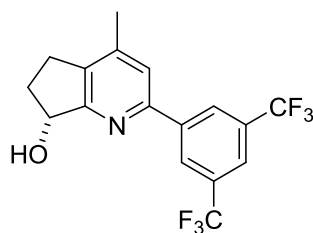


The reaction was set up as described in the general procedure **GP4** except using the analogous (*R*)-acetate (200 mg, 0.56 mmol, 1.00 eq.) in a mixture of MeOH:THF ((1:1), 4.0 mL) and 2 M NaOH (1.8 mL). Extraction afforded the product (141 mg, 0.45 mmol, 80%, 98.5% *ee*) as a colorless solid.

$\text{C}_{18}\text{H}_{21}\text{NO}_4$  (357.41 g/mol):

$[\alpha]_D^{20} = -14.4$  ( $c = 0.68$ ,  $\text{CHCl}_3$ ).

Additional analytical data match the racemic alcohol.

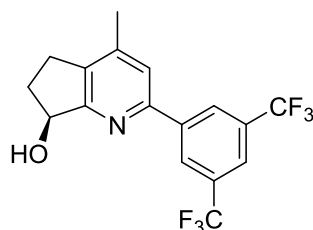
**(R)-2-(3,5-Bis(trifluoromethyl)phenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol**

The reaction was set up as described in the general procedure **GP4** except using the analogous (*R*)-acetate (103 mg, 0.26 mmol, 1.00 eq.) in a mixture of MeOH (5 mL) and 2 M NaOH (2.0 mL). Extraction afforded the product (85.0 mg, 0.23 mmol, 89%, 99.1% *ee*) as a colorless solid.

C<sub>17</sub>H<sub>13</sub>NF<sub>6</sub>NO (357.41 g/mol):

[ $\alpha$ ]<sub>D</sub><sup>20</sup> = +18.9 (c = 0.43, CHCl<sub>3</sub>).

Additional analytical data match the racemic alcohol.

**(S)-2-(3,5-Bis(trifluoromethyl)phenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol**

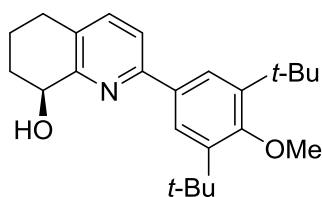
The reaction was set up as described in the general procedure **GP4** except using the analogous (*S*)-carboxylic acid (133 mg, 0.26 mmol, 1.00 eq.) in MeOH (5 mL) and 2 M NaOH (2.0 mL). The solution was stirred for 6 h at reflux. Extraction and workup afforded the product (86.0 mg, 0.24 mmol, 95%, 99.8% *ee*) as a colorless solid.

C<sub>17</sub>H<sub>13</sub>NF<sub>6</sub>NO (357.41 g/mol):

[ $\alpha$ ]<sub>D</sub><sup>20</sup> = −18.9 (c = 0.43, CHCl<sub>3</sub>).

Additional analytical data match the racemic alcohol.



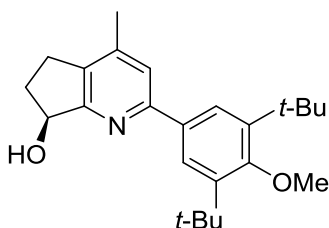
**(S)-2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-8-ol ((S)-2.51)**

The reaction was setup as described in the general procedure **GP3** for the racemic silyl ethers. Deprotection of the analogous (*S*)-TBS ether (300 mg, 6.23 mmol) afforded the product (190 mg, 5.17 mmol, 83%, 99.8% *ee*) as a colorless solid.

C<sub>24</sub>H<sub>33</sub>NO<sub>2</sub> (357.41 g/mol):

$[\alpha]_D^{20} = +97.5$  (*c* = 0.83, CHCl<sub>3</sub>).

Additional analytical data match the racemic alcohol.

**(S)-2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol**

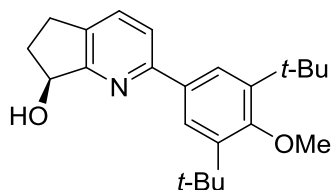
The reaction was setup as described in the general procedure **GP3** for the racemic silyl ethers. Deprotection of the analogous (*S*)-TBS ether (240 mg, 4.99 mmol) afforded the product (180 mg, 4.90 mmol, 98%, 99.8% *ee*) as a colorless solid.

C<sub>24</sub>H<sub>33</sub>NO<sub>2</sub> (357.41 g/mol):

$[\alpha]_D^{20} = +26.9$  (*c* = 0.50, CHCl<sub>3</sub>).

Additional analytical data match the racemic alcohol.

**(S)-2-(3,5-Di-tert-butyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol**  
**((S)-2.50)**



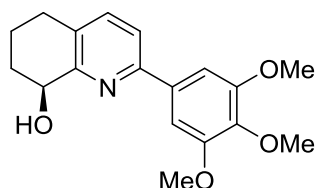
The reaction was setup as described in the general procedure **GP3** for the racemic silyl ethers. Deprotection of the analogous TBS ether (300 mg, 6.23 mmol) afforded the product (190 mg, 5.17 mmol, 83%, 99.8% *ee*) as a colorless solid.

$C_{23}H_{31}NO_2$  (354.24 g/mol):

$[\alpha]_D^{20} = +19.2$  ( $c = 0.39$ ,  $CHCl_3$ ).

Additional analytical data match the racemic alcohol **2.50**.

**(S)-2-(3,4,5-Trimethoxyphenyl)-5,6,7,8-tetrahydroquinolin-8-ol ((S)-2.51)**

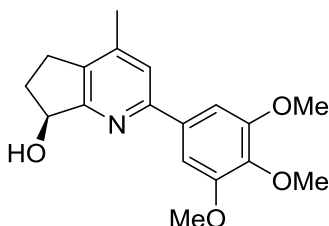


The reaction was setup as described in the general deprotection procedure **GP3** of the racemic silyl ethers. Deprotection of analogous TBS ether (120 mg, 2.79 mmol) afforded the product (57.0 mg, 1.81 mmol, 65%, 99.8% *ee*) as a colorless solid.

$C_{18}H_{21}NO_4$  (315.37 g/mol):

$[\alpha]_D^{20} = +106.4$  ( $c = 0.75$ ,  $CHCl_3$ ).

Additional analytical data match the racemic alcohol.

**(S)-4-Methyl-2-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol ((S)-2.52)**

The reaction was setup as described in the general procedure **GP3** for the racemic silyl ethers. Deprotection of the analogous silyl ether (114 mg, 2.66 mmol) afforded the product (77.0 mg, 2.44 mmol, 92%, 99.7% *ee*) as a colorless solid.

C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub> (315.37 g/mol):

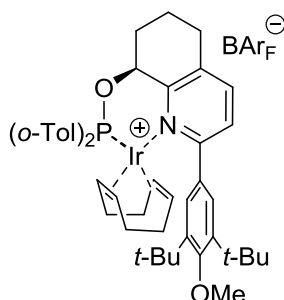
$[\alpha]_D^{20} = +14.9$  (*c* = 0.75, CHCl<sub>3</sub>).

Additional analytical data match the racemic alcohol ((*S*)-**2.52**).

## 8.2.2 Formation of N,P ligands followed by direct complexation

### General procedure: Synthesis of di-arylphosphinite based catalyst GP5

#### Iridium complex ((S)-2.62)



The pyridyl alcohol (*S*)-**2.41** (60.0 mg, 163  $\mu\text{mol}$ , 1.00 eq.), 4-dimethylaminopyridine (23.9 mg, 196  $\mu\text{mol}$ , 1.20 eq.) and chloro-di-(2-methylphenyl)-phosphine (50.4 mg, 196  $\mu\text{mol}$ , 1.20 eq.) were added into a dry Schlenk flask. This flask was evacuated and backfilled three times with argon.  $\text{CH}_2\text{Cl}_2$  (1.4 mL) was added to obtain a colorless solution which was stirred for 7 h at room temperature. A second pre-dried Schlenk flask was filled with  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (54.7 mg, 81.5  $\mu\text{mol}$ , 0.50 eq.),  $\text{NaBArF}_4$  (175 mg, 196  $\mu\text{mol}$ , 1.20 eq.) and equipped with a Schlenk frit. The frit was charged with basic aluminum oxide ( $d \times h$ :  $3 \times 2$  cm). The equipment was evaporated and backfilled with argon three times.

The ligand containing solution was added onto the frit and eluted with  $\text{CH}_2\text{Cl}_2$  (5 mL). The orange solution was stirred for 18 h at room temperature. The solvent was evaporated under reduced pressure and the crude iridium complex was concentrated and adsorbed onto silica (4 g). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 20$  cm, hexane: $\text{CH}_2\text{Cl}_2$  (1:1)) afforded the product (208 mg, 119  $\mu\text{mol}$ , 73%) as an orange solid.

$\text{C}_{78}\text{H}_{70}\text{BF}_{24}\text{IrNO}_2\text{P}$  (1743.39 g/mol):

**MP:** 90-91  $^\circ\text{C}$ .

**TLC:**  $R_f$  = 0.29 ( $\text{SiO}_2$ , hexane: $\text{CH}_2\text{Cl}_2$  (1:1), UV).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.96 (dd,  $J_{\text{HH}}$  = 18, 7 Hz, 1H, ar-*H*), 7.70 (s, 8H,  $\text{BArF}_4$ ), 7.61 (s, 2H, ar-*H*), 7.49 (s, 4H,  $\text{BArF}_4$ ), 7.49-7.47 (m, 1H, ar-*H*), 7.36-7.32 (m, 3H, ar-*H*), 7.26-7.22 (m, 2H, ar-*H*), 7.18 (t,  $J_{\text{HH}}$  = 7.6 Hz, 1H, ar-*H*), 7.14 (dd,  $J_{\text{HH}}$  = 7.3, 2.0 Hz, 1H, ar-*H*), 6.92-6.89 (m, 1H, ar-*H*), 6.37-6.36 (m, 1H, HCOP), 5.02 (s br, 1H, CH COD), 3.96 (s br, 1H, CH COD), 3.82 (s, 3H,  $\text{OCH}_3$ ), 3.12-3.06 (m, 1H, CH COD), 2.85-2.75 (m, 2H, CH COD and

$\text{CH}_2$ ), 2.70-2.63 (m, 2H,  $\text{CH}_2$ ), 2.36 (s, 3H, ar- $\text{CH}_3$ ), 2.25-2.18 (m, 2H,  $\text{CH}_2$ ), 2.12-2.08 (m, 2H,  $\text{CH}_2$  and  $\text{CH}_2$  COD), 2.05 (s, 3H, ar- $\text{CH}_3$ ), 1.94-1.78 (m, 4H,  $\text{CH}_2$  COD), 1.53 (s, 18H,  $2 \times \text{C}(\text{CH}_3)_3$ ), 1.30-1.19 (m, 3H,  $\text{CH}_2$  COD).

$^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 162.2$  (s, ar-C), 161.9 (q,  $J_{\text{BC}} = 50$  Hz,  $\text{BAr}_\text{F}$ ), 161.7 (s, ar-C), 153.3 (d,  $J_{\text{CP}} = 3$  Hz, ar-C), 145.4 (s, ar-C), 142.6 (s, ar-C), 141.0 (s, ar-C), 140.2 (d,  $J_{\text{CP}} = 9$  Hz, ar-C), 135.7 (s, ar-C), 135.3 (s, ar-C), 135.0 (s,  $\text{BAr}_\text{F}$ ), 134.6 (s, ar-C), 134.1 (s, ar-C), 133.8 (s, ar-C), 133.3 (d,  $J_{\text{CP}} = 7$  Hz, ar-C), 132.9 (s, ar-C), 132.2 (s, ar-C), 132.1 (s, ar-C), 130.8 (d,  $J_{\text{CP}} = 12$  Hz, ar-C), 129.9 (s, ar-C), 129.1 (qq,  $J_{\text{CF}} = 30$  Hz,  $J_{\text{CF}} = 3$  Hz,  $\text{BAr}_\text{F}$ ), 127.1 (s, ar-C), 126.5 (d,  $J_{\text{CP}} = 11$  Hz, ar-C), 125.2 (d,  $J_{\text{CP}} = 17$  Hz, ar-C), 124.7 (q,  $J_{\text{CF}} = 273$  Hz,  $\text{BAr}_\text{F}$   $\text{CF}_3$ ), 117.6 (sept,  $J_{\text{CF}} = 4$  Hz,  $\text{BAr}_\text{F}$ ), 97.6 (d,  $J_{\text{CP}} = 8$  Hz, CH COD), 90.5 (d,  $J_{\text{CP}} = 15$  Hz, CH COD), 76.1 (s, COP), 69.2 (s, CH COD), 64.8 (s,  $\text{OCH}_3$ ), 64.0 (s, CH COD), 37.3 (d,  $J_{\text{CP}} = 10$  Hz,  $\text{CH}_2$ ), 36.5 (s,  $\text{C}(\text{CH}_3)_3$ ), 33.9 (s,  $\text{CH}_2$  COD), 32.1 (s,  $2 \times \text{C}(\text{CH}_3)_3$ ), 30.5 (d,  $J_{\text{CP}} = 10$  Hz,  $\text{CH}_2$ , COD), 28.6 (s,  $\text{CH}_2$  COD), 28.2 (s,  $\text{CH}_2$ ), 25.1 (s,  $\text{CH}_2$  COD), 22.0 (d,  $J_{\text{CP}} = 5$  Hz, ar- $\text{CH}_3$ ), 21.4 (d,  $J_{\text{CP}} = 3$  Hz, ar- $\text{CH}_3$ ), 17.3 (s,  $\text{CH}_2$ ).

$^{31}\text{P}\{^1\text{H}\}$  NMR (161 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 103.3$  (s).

$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = -62.7$  (s).

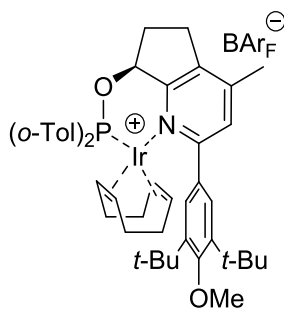
$^{11}\text{B}\{^1\text{H}\}$  NMR (160 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = -6.6$  (s).

IR (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 2961$  (w), 2939 (w), 2889 (w), 2876 (w), 1609 (w), 1454 (w), 1353 (m), 1273 (s), 1160 (m), 1117 (s), 1003 (m), 930 (m), 885 (m), 838 (m), 713 (m), 669 (m).

MS (FAB NBA):  $m/z$  (%): 882.3 (13), 881.3 (49), 880.3 (100), 879.3 (31), 878.3 (60), 771.2 (12), 770.1 (17), 769.1 (17), 768.2 (23), 767.1 (20), 766.1 (32), 765.1 (18), 764.1 (28), 763.1 (11), 762.1 (18), 760.1 (10), 418.9 (12), 417.0 (11).

EA ( $\text{C}_{78}\text{H}_{20}\text{BF}_{24}\text{IrNO}_2\text{P}$ ): calc.: C 53.74, H 4.05, N 0.80; found: C 53.97, H 4.22, N 0.91.

$[\alpha]_D^{20} = +68.2$  (c = 0.92,  $\text{CHCl}_3$ ).

**Iridium complex ((S)-2.61)**

The reaction was set up as described in the general procedure **GP5** except using the analogous (S)-pyridyl alcohol (40.0 mg, 109  $\mu$ mol, 1.00 eq.), 4-dimethylaminopyridine (17.0 mg, 130  $\mu$ mol, 1.20 eq.) and chloro-di-(2-methylphenyl)-phosphine (34.0 mg, 130  $\mu$ mol, 1.20 eq.) in abs.  $\text{CH}_2\text{Cl}_2$  (2 mL). This solution was filtered into  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (37.0 mg, 109  $\mu$ mol, 1.00 eq.) and  $\text{NaBArF}$  (117 mg, 130  $\mu$ mol, 1.20 eq.). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 20$  cm, hexane: $\text{CH}_2\text{Cl}_2$  (1:1)) afforded the product (130 mg, 74.6  $\mu$ mol, 68%) as an orange solid.

$\text{C}_{78}\text{H}_{70}\text{BF}_{24}\text{IrNO}_2\text{P}$  (1743.39 g/mol):

**MP:** 96-99  $^\circ\text{C}$ .

**TLC:**  $R_f = 0.58$  ( $\text{SiO}_2$ , hexane: $\text{CH}_2\text{Cl}_2$  (1:2), UV).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm} = 8.32$  (d,  $J_{\text{HH}} = 14$  Hz, 1H, ar-*H*), 7.75 (s, 8H,  $\text{BArF}$ ), 7.57 (s, 6H,  $\text{BArF}$  and ar-*H*), 7.45 (s, 2H, ar-*H*), 7.39-7.36 (m, 1H, ar-*H*), 7.33 (s, 2H, ar-*H*), 7.23 (s, 1H, ar-*H*), 7.15-7.11 (m, 1H, ar-*H*), 6.69 (s, 1H, ar-*H*), 6.36 (s br, 1H, *HCOP*), 4.98 (s, 1H, *CH COD*), 3.83 (s, 3H,  $\text{OCH}_3$ ), 3.80 (s, 1H, *CH COD*), 3.14-3.0 (m, 2H, *CH COD* and  $\text{CH}_2$ ), 2.95-2.85 (m, 2H,  $\text{CH}_2$ ), 2.67 (s, 1H, *CH COD*), 2.59 (s, 3H,  $\text{CH}_3$ ), 2.51-2.49 (m, 1H,  $\text{CH}_2$ ), 2.35 (s, 4H,  $\text{CH}_3$  and  $\text{CH}_2$  *COD*), 2.28-2.21 (m, 2H,  $\text{CH}_2$  *COD*), 2.11 (s, 3H,  $\text{CH}_3$ ), 2.10-2.04 (m, 1H,  $\text{CH}_2$  *COD*), 1.89-1.83 (m, 1H,  $\text{CH}_2$  *COD*), 1.58 (s, 18H,  $2 \times \text{C}(\text{CH}_3)_3$ ), 1.45-1.30 (m, 3H,  $\text{CH}_2$  *COD*).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (126 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm} = 162.8$  (s, ar-*C*), 162.5 (s, ar-*C*), 162.3 (q,  $J_{\text{CB}} = 50$  Hz,  $\text{BArF}$ ), 159.3 (d,  $J_{\text{CP}} = 5$  Hz, ar-*C*), 150.1 (s, ar-*C*), 145.7 (s, ar-*C*), 143.3 (s, ar-*C*), 141.4 (d,  $J_{\text{CP}} = 8$  Hz, ar-*C*), 138.9 (s, ar-*C*), 137.1 (d,  $J_{\text{CP}} = 34$  Hz, ar-*C*), 136.0 (s, ar-*C*), 135.4 (s, 4H,  $\text{BArF}$ ), 134.3 (s, ar-*C*), 133.6 (d,  $J_{\text{CP}} = 8$  Hz, ar-*C*), 133.3 (d,  $J_{\text{CP}} = 1$  Hz, ar-*C*), 132.5 (d,  $J_{\text{CP}} = 8$  Hz, ar-*C*), 132.4 (d,  $J_{\text{CP}} = 2$  Hz, ar-*C*), 131.4 (d,  $J_{\text{CP}} = 14$  Hz, ar-*C*), 131.1 (s, ar-*C*), 129.5 (qq,  $J_{\text{CF}} = 32, 4$  Hz,  $\text{BArF}$ ), 128.9 (s, ar-*C*), 128.2 (s, ar-*C*), 126.6 (d,  $J_{\text{CP}} = 11$  Hz, ar-*C*), 125.9 (d,  $J_{\text{CP}} = 17$  Hz, ar-*C*), 125.2 (q,  $J_{\text{CF}} = 272$  Hz,  $\text{BArF CF}_3$ ), 118.1 (sept,  $J_{\text{CF}} = 4$  Hz,  $\text{BArF}$ ), 100.0 (d,  $J_{\text{CP}} = 10$  Hz, *CH COD*), 94.0 (d,  $J_{\text{CP}} = 14$  Hz, *CH COD*), 84.5 (s, *COP*),

67.9 (s, CH COD), 65.4 (s, OCH<sub>3</sub>), 63.1 (s, CH COD), 37.8 (d,  $J_{CP}$  = 3 Hz, CH<sub>2</sub> COD), 36.8 (s, C(CH<sub>3</sub>)<sub>3</sub>), 34.1 (s, CH<sub>2</sub> COD), 32.5 (s, C(CH<sub>3</sub>)<sub>3</sub>), 29.9 (d,  $J_{CP}$  = 10 Hz, CH<sub>2</sub>), 28.5 (s, CH<sub>2</sub> COD), 26.9 (s, CH<sub>2</sub>), 26.0 (s, CH<sub>2</sub> COD), 23.0 (d,  $J_{CP}$  = 4 Hz, CH<sub>3</sub>), 21.9 (d,  $J_{CP}$  = 3 Hz, CH<sub>3</sub>), 19.1 (s, CH<sub>3</sub>).

<sup>31</sup>P{<sup>1</sup>H} NMR (161 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = 111.1 (s).

<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = -63.1 (s).

<sup>11</sup>B{<sup>1</sup>H} NMR (160 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = -5.7 (s).

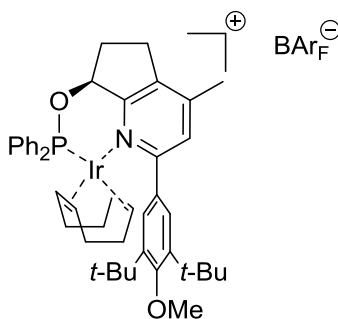
IR (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2957 (w), 1611 (w), 1461 (w), 1352 (m), 1271 (m), 1115 (s), 1012 (w), 959 (w), 886 (m), 824 (w), 719 (m), 670 (m).

MS (FAB NBA):  $m/z$  (%): 882.3 (13), 881.3 (49), 880.3 (100), 879.3 (31), 878.3 (58), 771.2 (12), 770.2 (24), 769.1 (20), 768.2 (31), 767.1 (25), 766.2 (38), 765.1 (21), 674.1 (28), 763.1 (13), 762.1 (18), 760.1 (10), 419 (10), 350 (12).

EA (C<sub>78</sub>H<sub>20</sub>BF<sub>24</sub>IrNO<sub>2</sub>P): calc.: C 53.74, H 4.05, N 0.80; found: C 53.80, H 4.14, N 0.95.

$[\alpha]_D^{20}$  = +63.3 (c = 0.94, CHCl<sub>3</sub>).

### Iridium complex ((S)-2.60)



The reaction was set up as described in the general procedure **GP5** except using the analogous (S)-pyridyl alcohol (35 mg, 95 μmol, 1.00 eq.), 4-dimethylaminopyridine (14 mg, 114 μmol, 1.20 eq.) and chloro-di-phenyl-phosphine (21 μL, 114 μmol, 1.20 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). This solution was filtered into [Ir(COD)Cl]<sub>2</sub> (34 mg, 95 μmol, 1.00 eq.) and NaBArF (104 mg, 114 μmol, 1.20 eq.). Column chromatography (SiO<sub>2</sub>, d × h: 3 × 20 cm, hexane:CH<sub>2</sub>Cl<sub>2</sub> (1:1)) afforded the product (47 mg, 28 μmol, 29%) as an orange solid.

C<sub>76</sub>H<sub>66</sub>BF<sub>24</sub>IrNO<sub>2</sub>P (1715.33 g/mol):

MP: 81-84 °C.

TLC: R<sub>f</sub> = 0.43 (SiO<sub>2</sub>, hexane:CH<sub>2</sub>Cl<sub>2</sub> (1:1), UV).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 7.75 (s, 8H,  $\text{BAr}_\text{F}$ ), 7.57-7.54 (m, 9H, ar-*H* and  $\text{BAr}_\text{F}$ ), 7.46 (s, 1H, ar-*H*), 7.43-7.40 (m, 5H, ar-*H*), 7.35-7.32 (m, 2H, ar-*H*), 6.43-6.39 (m, 1H, *HCOP*), 4.65 (s br, 1H, *CH COD*), 4.21 (s br, 1H, *CH COD*), 3.77 (s, 3H,  $\text{OCH}_3$ ), 3.23-3.12 (m, 3H, *CH COD* and  $\text{CH}_2$ ), 3.07-2.98 (m, 2H,  $\text{CH}_2$ ), 2.66-2.59 (m, 1H,  $\text{CH}_2$ ), 2.46 (s, 3H,  $\text{CH}_3$ ), 2.27-2.23 (m, 2H,  $\text{CH}_2 \text{ COD}$ ), 2.17-2.08 (m, 1H,  $\text{CH}_2 \text{ COD}$ ), 1.97-1.85 (m, 2H,  $\text{CH}_2 \text{ COD}$ ), 1.40 (s, 18H,  $2 \times \text{C}(\text{CH}_3)_3$ ), 1.34-1.22 (m, 2H,  $\text{CH}_2 \text{ COD}$ ), 0.90-0.83 (m, 1H,  $\text{CH}_2 \text{ COD}$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (126 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 162.9 (s, ar-*C*), 162.4 (q,  $J_{\text{CB}} = 50 \text{ Hz}$ ,  $\text{BAr}_\text{F}$ ), 162.4 (s, ar-*C*), 159.9 (d,  $J_{\text{CP}} = 4 \text{ Hz}$ , ar-*C*), 150.3 (s, ar-*C*), 146.2 (s, ar-*C*), 138.6 (s, ar-*C*), 136.4 (d,  $J_{\text{CP}} = 56 \text{ Hz}$ , ar-*C*), 135.4 (s,  $\text{BAr}_\text{F}$ ), 134.0 (s), 132.4 (d,  $J_{\text{CP}} = 2 \text{ Hz}$ , ar-*C*), 132.3 (d,  $J_{\text{CP}} = 2 \text{ Hz}$ , ar-*C*), 131.1 (d,  $J_{\text{CP}} = 62 \text{ Hz}$ , ar-*C*), 130.6 (d,  $J_{\text{CP}} = 13 \text{ Hz}$ , ar-*C*), 130.2 (d,  $J_{\text{CP}} = 11 \text{ Hz}$ , ar-*C*), 129.9 (d,  $J_{\text{CP}} = 7 \text{ Hz}$ , ar-*C*), 129.9 (s, ar-*C*), 129.6 (d,  $J_{\text{CP}} = 11 \text{ Hz}$ , ar-*C*), 129.5 (qq,  $J_{\text{CF}} = 30, 3 \text{ Hz}$ ,  $\text{BAr}_\text{F}$ ), 127.0 (s, ar-*C*), 125.2 (q,  $J_{\text{CF}} = 272 \text{ Hz}$ ,  $\text{BAr}_\text{F} \text{ CF}_3$ ), 118.1 (sept,  $J_{\text{CF}} = 4 \text{ Hz}$ ,  $\text{BAr}_\text{F}$ ), 100.3 (d,  $J_{\text{CP}} = 10 \text{ Hz}$ , *CH COD*), 92.8 (d,  $J_{\text{CP}} = 14 \text{ Hz}$ , *CH COD*), 85.6 (s, *COP*) 69.3 (s, *CH COD*), 65.3 (s,  $\text{OCH}_3$ ), 61.9 (s, *CH COD*), 37.1 (d,  $J_{\text{CP}} = 3 \text{ Hz}$ ,  $\text{CH}_2 \text{ COD}$ ), 36.6 (s,  $\text{C}(\text{CH}_3)_3$ ), 33.6 (s,  $\text{CH}_2 \text{ COD}$ ), 32.3 (s,  $\text{C}(\text{CH}_3)_3$ ), 30.2 (d,  $J_{\text{CP}} = 3 \text{ Hz}$ ,  $\text{CH}_2$ ), 29.4 (s,  $\text{CH}_2 \text{ COD}$ ), 27.1 (s,  $\text{CH}_2$ ), 25.9 (s,  $\text{CH}_2 \text{ COD}$ ), 19.3 (s,  $\text{CH}_3$ ).

**$^{31}\text{P}\{^1\text{H}\}$  NMR** (161 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 96.5 (s).

**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = -63.1 (s).

**$^{11}\text{B}\{^1\text{H}\}$  NMR** (160 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = -6.6 (s).

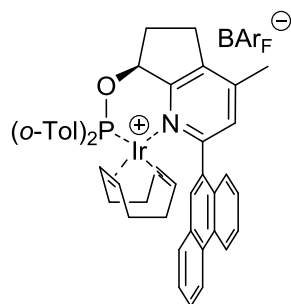
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2962 (w), 1920 (w), 2851 (w), 1716 (m), 1597 (m), 1387 (m), 1352 (m), 1278 (s), 1258 (m), 1163 (m), 1120 (s), 1024 (m), 894 (m), 678 (m).

**MS** (FAB NBA):  $m/z$  (%): 854.3 (13), 853.3 (47), 852.3 (100), 851.3 (34), 850.2 (65), 740.1 (10), 739.1 (12).

**EA** ( $\text{C}_{76}\text{H}_{66}\text{BF}_{24}\text{IrNO}_2\text{P}$ ): calc.: C 53.22, H 3.88, N 0.82; found: C 53.44, H 4.15, N 1.01.

**$[\alpha]_D^{20}$**  = +16.5 ( $c = 0.41$ ,  $\text{CHCl}_3$ ).



**Iridium complex ((S)-2.68)**

The reaction was set up as described in the general procedure **GP5** except using the pyridyl alcohol (**S**)-**2.57** (30 mg, 92  $\mu\text{mol}$ , 1.00 eq.), 4-dimethylaminopyridine (14 mg, 114  $\mu\text{mol}$ , 1.20 eq.) and chloro-di-(2-methylphenyl)-phosphine (28 mg, 111  $\mu\text{mol}$ , 1.20 eq.) in  $\text{CH}_2\text{Cl}_2$  (0.8 mL). This solution was filtered into  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (31 mg, 46  $\mu\text{mol}$ , 0.50 eq.) and  $\text{NaBArF}$  (98 mg, 111  $\mu\text{mol}$ , 1.20 eq.). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 20$  cm,  $\text{CH}_2\text{Cl}_2$ ) afforded the product (77 mg, 45  $\mu\text{mol}$ , 49%) as an orange solid.

$\text{C}_{77}\text{H}_{56}\text{BF}_4\text{IrNOP}$  (1701.26 g/mol):

**MP**: 105-106  $^\circ\text{C}$ .

**TLC**:  $R_f = 0.85$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 8.90 (d,  $J = 8.5$  Hz, 1H), 8.88-8.84 (m, 1H), 8.26-8.19 (m, 1H), 7.94-7.85 (m, 3H), 7.84-7.78 (m, 2H), 7.78-7.75 (m, 2H), 7.74 (s, 8H), 7.70-7.65 (m, 1H), 7.60 (dd,  $J = 4.6, 2.8$  Hz, 1H), 7.56 (s, 4H), 7.52 (s, 1H), 7.43-7.34 (m, 3H), 7.14-7.07 (m, 1H), 6.58 (t,  $J = 10.5$  Hz, 1H), 6.38-6.30 (m, 1H), 5.07-4.97 (m, 1H), 4.11-3.98 (m, 1H), 3.22-3.14 (m, 1H), 3.10-3.03 (m, 1H), 3.03-2.88 (m, 2H), 2.81 (s, 3H), 2.64-2.50 (m, 2H), 2.43 (s, 3H), 2.39-2.20 (m, 4H), 1.97-1.87 (m, 1H), 1.85-1.75 (m, 1H), 1.72-1.61 (m, 1H), 1.16 (s, 2H), 1.01-0.85 (m, 1H), 0.35-0.23 (m, 1H).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 162.3 (q,  $J_{\text{CB}} = 50$  Hz,  $\text{BArF}$ ), 160.4 (d,  $J_{\text{CP}} = 4$  Hz, ar-C), 159.3 (s, ar-C), 149.4 (s, ar-C), 141.6 (d,  $J_{\text{CP}} = 8$  Hz, ar-C), 139.7 (s, ar-C), 135.9 (s, ar-C), 135.7 (s, ar-C), 135.4 (s,  $\text{BArF}$ ), 133.7 (d,  $J_{\text{CP}} = 7$  Hz, ar-C), 133.4 (s, ar-C), 132.6 (s, ar-C), 132.5 (d,  $J_{\text{CP}} = 7$  Hz, ar-C), 132.2 (s, ar-C), 131.6 (s, ar-C), 131.5 (d,  $J_{\text{CP}} = 14$  Hz, ar-C), 131.1 (s, ar-C), 130.8 (s, ar-C), 130.5 (s, ar-C), 129.5 (s, ar-C), 129.4 (qq,  $J_{\text{CF}} = 32, 3$  Hz,  $\text{BArF}$ ), 128.8 (s, ar-C), 128.8 (s, ar-C), 128.7 (s, ar-C), 128.6 (s, ar-C), 128.5 (s, ar-C), 126.7 (d,  $J_{\text{CP}} = 12$  Hz, ar-C), 126.2 (s, ar-C), 125.2 (q,  $J_{\text{CF}} = 273$  Hz,  $\text{BArF}$ ), 124.3 (s, ar-C), 123.9 (s, ar-C), 118.1 (sept,  $J_{\text{CF}} = 4$  Hz,  $\text{BArF}$ ), 98.3-98.1 (m, CH COD), 89.0-88.7 (m, CH COD), 84.1 (s, COP), 68.4 (s, CH COD), 66.2 (s, CH COD), 36.5 (d,  $J_{\text{CP}} = 4$  Hz,  $\text{CH}_2$  COD), 35.0 (s,

CH<sub>2</sub>), 29.8 (d,  $J_{CP}$  = 10 Hz, CH<sub>2</sub> COD), 28.3 (s, CH<sub>2</sub> COD), 27.3 (s, CH<sub>2</sub>), 24.4 (d,  $J_{CP}$  = 4 Hz, CH<sub>2</sub> COD), 23.3 (d,  $J_{CP}$  = 4 Hz, CH<sub>3</sub>), 22.9-22.8 (m, CH<sub>3</sub>), 19.3 (s, CH<sub>3</sub>).

<sup>31</sup>P{<sup>1</sup>H} NMR (202 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 234 K): δ/ppm = 113.3 (s), 101.3 (s).

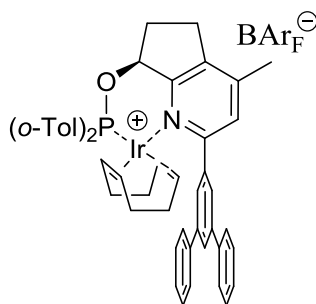
<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = -62.8 (s)

IR (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3060 (w), 3004 (w), 2880 (w), 2023 (w), 1967 (w), 1612 (w), 1566 (w), 1354 (m), 1274 (s), 1118 (s), 1004 (w), 959 (w), 887 (m), 839 (m), 806 (w), 753 (m), 713 (m), 679 (m), 619 (w).

HRMS (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for C<sub>45</sub>H<sub>44</sub>IrNOP<sup>+</sup>: 838.2787 [M-BAr<sub>F</sub>]<sup>+</sup>; found: 838.2781.

[ $\alpha$ ]<sub>D</sub><sup>20</sup> = +15.1 (c = 0.20, CHCl<sub>3</sub>).

### Iridium complex ((*S*)-2.65)



The reaction was set up as described in the general procedure **GP5** except using the pyridyl alcohol (*S*)-**2.54** (30 mg, 80 μmol, 1.00 eq.), 4-dimethylaminopyridine (12 mg, 95 μmol, 1.20 eq.) and chloro-di-(2-methylphenyl)-phosphine (24 mg, 95 μmol, 1.20eq.) in abs. CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL). This solution was filtered into [Ir(COD)Cl]<sub>2</sub> (27 mg, 40 μmol, 0.50 eq.) and NaBAr<sub>F</sub> (85 mg, 95 μmol, 1.20 eq.). Column chromatography (SiO<sub>2</sub>, d × h: 3 × 20 cm, pentane:Et<sub>2</sub>O (1:1) → CH<sub>2</sub>Cl<sub>2</sub>) afforded the product (106 mg, 60 μmol, 76%) as an orange solid.

C<sub>81</sub>H<sub>60</sub>BF<sub>24</sub>IrNOP (1753.34 g/mol):

MP: 103-104 °C.

TLC: R<sub>f</sub> = 0.89 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, UV).

<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = 8.13-7.92 (m, 4H), 7.78-7.72 (m, 13H), 7.67-7.48 (m, 10H), 7.45 (td,  $J$  = 7.5, 1.8 Hz, 1H), 7.40-7.30 (m, 2H), 7.28-7.15 (m, 2H), 7.10-7.03 (m, 1H), 6.50 (dd,  $J$  = 13.5, 8.0 Hz, 1H), 6.39-6.32 (m, 1H), 4.94 (d,  $J$  = 8.0 Hz, 1H), 3.87 (t,  $J$  = 6.0 Hz, 1H), 3.30-3.08 (m, 2H), 3.05-2.89 (m, 2H), 2.72 (s, 3H), 2.65 (dd,  $J$  = 14.6, 6.9 Hz,

1H), 2.54-2.45 (m, 1H), 2.44 (s, 3H), 2.37-2.19 (m, 1H), 2.12 (s, 3H), 2.07-1.77 (m, 4H), 1.40-1.22 (m, 3H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 162.3 (q,  $J_{\text{CB}}$  = 50 Hz,  $\text{BAr}_\text{F}$ ), 161.4 (s, ar-C), 160.1 (d,  $J_{\text{CP}}$  = 4 Hz, ar-C), 150.6 (s, ar-C), 144.0 (s, ar-C), 141.5 (d,  $J_{\text{CP}}$  = 8 Hz, ar-C), 140.7 (s, ar-C), 140.5 (s, ar-C), 139.3 (s, ar-C), 135.4 (d,  $J_{\text{CP}}$  = 56 Hz, ar-C), 135.4 (s,  $\text{BAr}_\text{F}$ ), 133.6 (d,  $J_{\text{CP}}$  = 7 Hz, ar-C), 133.1 (d,  $J_{\text{CP}}$  = 2 Hz, ar-C), 132.6-132.4 (m, ar-C), 131.4 (d,  $J_{\text{CP}}$  = 14 Hz, ar-C), 130.2 (s, ar-C), 129.8 (s, ar-C), 129.8 (s, ar-C), 129.4 (qq,  $J_{\text{CF}}$  = 32 Hz, 3 Hz,  $\text{BAr}_\text{F}$ ), 129.1 (s, ar-C), 128.1 (s, ar-C), 126.8 (s, ar-C), 126.7 (d,  $J_{\text{CP}}$  = 12 Hz), 126.2 (d,  $J_{\text{CP}}$  = 16 Hz, ar-C), 125.2 (q,  $J_{\text{CF}}$  = 274 Hz,  $\text{BAr}_\text{F}$ ), 118.1 (sept,  $J_{\text{CF}}$  = 4 Hz,  $\text{BAr}_\text{F}$ ), 99.6 (d,  $J_{\text{CP}}$  = 8 Hz, ar-C), 91.3 (d,  $J_{\text{CP}}$  = 16 Hz, ar-C), 84.3 (s, COD), 68.6 (s, CH COD), 66.2-66.0 (m, CH COD), 37.2 (d,  $J_{\text{CP}}$  = 3 Hz,  $\text{CH}_2$  COD), 34.6 (s,  $\text{CH}_2$ ), 30.0 (d,  $J_{\text{CP}}$  = 10 Hz,  $\text{CH}_2$  COD), 28.4 (d,  $J_{\text{CP}}$  = 2 Hz,  $\text{CH}_2$  COD), 26.8 (s,  $\text{CH}_2$ ), 25.6 (d,  $J_{\text{CP}}$  = 2 Hz,  $\text{CH}_2$  COD), 23.1 (d,  $J_{\text{CP}}$  = 5 Hz,  $\text{CH}_3$ ), 22.5 (d,  $J_{\text{CP}}$  = 3 Hz,  $\text{CH}_3$ ), 19.3 (s,  $\text{CH}_3$ ).

$^{31}\text{P}\{^1\text{H}\}$  NMR (202 MHz,  $\text{CD}_2\text{Cl}_2$ , 234 K):  $\delta/\text{ppm}$  = 113.3 (s), 100.8 (s).

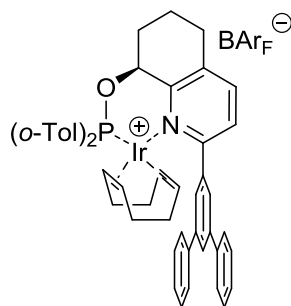
$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = -62.8 (s).

IR (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2977 (w), 2888 (w), 1611 (w), 1455 (w), 1354 (m), 1274 (s), 1119 (s), 966 (w), 886 (m), 839 (m), 821 (w), 757 (m), 712 (m), 679 (m).

HRMS (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{49}\text{H}_{48}\text{IrNOP}^+$ : 890.3101 [ $\text{M}-\text{BAr}_\text{F}$ ] $^+$ ; found: 890.3103.

$[\alpha]_D^{20}$  = +36.0 ( $c$  = 0.24,  $\text{CHCl}_3$ ).

### Iridium complex ((*S*)-2.66)



The reaction was set up as described in the general procedure **GP5** except using the pyridyl alcohol (*S*)-**2.55** ((42 mg, 112  $\mu\text{mol}$ , 1.00 eq.), 4-dimethylaminopyridine (20 mg, 134  $\mu\text{mol}$ , 1.20 eq.) and chloro-di-(2-methylphenyl)-phosphine (40 mg, 134  $\mu\text{mol}$ , 1.20 eq.) in abs.  $\text{CH}_2\text{Cl}_2$  (3.4 mL). This solution was filtered into  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (44 mg, 56  $\mu\text{mol}$ , 0.50 eq.) and

NaBAr<sub>F</sub> (137 mg, 134 μmol, 1.20 eq.). Column chromatography (SiO<sub>2</sub>, d × h: 3 × 20 cm, pentane:Et<sub>2</sub>O (4:1) → Et<sub>2</sub>O → CH<sub>2</sub>Cl<sub>2</sub>) afforded the product (141 mg, 80.6 μmol, 72%) as an orange solid.

C<sub>81</sub>H<sub>60</sub>BF<sub>24</sub>IrNOP (1753.34 g/mol):

**MP:** 107-108 °C.

**TLC:** R<sub>f</sub> = 0.32 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (4:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = 7.98 (d, *J* = 1.8 Hz, 1H), 7.76 (s, 2H), 7.72-7.58 (m, 12H), 7.52-7.47 (m, 8H), 7.45-7.40 (m, 2H), 7.37-7.32 (m, 1H), 7.31-7.23 (m, 2H), 7.16-7.13 (m, 1H), 7.10-7.02 (m, 2H), 6.70-6.65 (m, 1H), 6.22-6.19 (m, 1H), 5.28-5.24 (m, 3H), 4.86 (s br, 1H), 4.08 (s br, 1H), 3.10-3.05 (m, 1H), 2.96-2.89 (m, 2H), 2.83-2.75 (m, 1H), 2.61 (s, 3H), 2.56 (s, 1H), 2.30-2.19 (m, 2H), 1.99-1.64 (m, 9H), 1.26-1.06 (m, 3H).

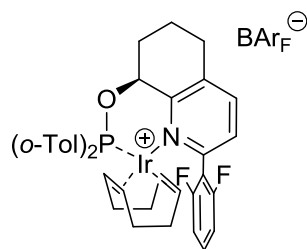
**<sup>13</sup>C{<sup>1</sup>H} NMR** (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = 162.1 (q, *J*<sub>BC</sub> = 50 Hz, BAr<sub>F</sub>), 160.8 (s, ar-C), 154.3 (d, *J*<sub>CP</sub> = 2 Hz, ar-C), 144.0 (s, ar-C), 141.8 (d, *J*<sub>CP</sub> = 7 Hz, ar-C), 141.5 (s, ar-C), 141.3 (d, *J*<sub>CP</sub> = 10 Hz, ar-C), 140.3 (s, ar-C), 140.2 (s, ar-C), 136.8 (s, ar-C), 135.2 (s, BAr<sub>F</sub>), 134.7 (s, ar-C), 134.2 (s, ar-C), 133.3 (d, *J*<sub>CP</sub> = 8 Hz, ar-C), 132.5 (d, *J*<sub>CP</sub> = 2 Hz, ar-C), 132.4-132.3 (m, ar-C), 131.4 (d, *J*<sub>CP</sub> = 13 Hz, ar-C), 130.0 (s, ar-C), 129.7 (s, ar-C), 129.2 (qq, *J*<sub>CF</sub> = 31 Hz, *J*<sub>CF</sub> = 2.8 Hz, BAr<sub>F</sub>), 129.0 (s, ar-C), 127.9 (s, ar-C), 127.6 (s, ar-C), 126.6 (d, *J*<sub>CP</sub> = 11 Hz, ar-C), 126.3 (s, ar-C), 126.3 (d, *J*<sub>CP</sub> = 17 Hz, ar-C), 124.8 (q, *J*<sub>CF</sub> = 273 Hz, BAr<sub>F</sub> CF<sub>3</sub>), 117.9 (sept, *J*<sub>CF</sub> = 4 Hz, BAr<sub>F</sub>), 95.9 (d, *J*<sub>CP</sub> = 7 Hz, CH COD), 85.3 (d, *J*<sub>CP</sub> = 17 Hz, CH COD), 76.2 (s, COP), 69.8 (s, CH COD), 54.3 (s, OCH<sub>3</sub>), 54.0 (s, CH COD), 36.7 (d, *J*<sub>CP</sub> = 4 Hz, CH<sub>2</sub>), 34.9 (s, CH<sub>2</sub> COD), 30.9 (d, *J*<sub>CP</sub> = 10 Hz, CH<sub>2</sub>, COD), 29.1 (s, CH<sub>2</sub> COD), 28.5 (s, CH<sub>2</sub>), 24.7 (d, *J*<sub>CP</sub> = 3 Hz, CH<sub>2</sub> COD), 22.4 (d, *J*<sub>CP</sub> = 5 Hz, ar-CH<sub>3</sub>), 22.2 (d, *J*<sub>CP</sub> = 6 Hz, ar-CH<sub>3</sub>), 16.3 (s, CH<sub>2</sub>).

**<sup>31</sup>P{<sup>1</sup>H} NMR** (162 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = 100.1 (s).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3059 (w), 2927 (w), 1593 (w), 1565 (w), 1498 (w), 1473 (w), 1454 (w), 1353 (w), 1273 (s), 1117 (s), 1029 (s), 999 (m), 966 (m), 931 (m), 884 (m), 868 (m), 838 (m), 806 (m), 755 (m), 711 (m), 697 (m), 681 (m), 669 (m), 613 (w), 599 (w), 569 (m), 534 (m), 505 (w), 477 (m), 449 (m).

**HRMS** (ESI, 4500 V, 180 °C): (*m/z*) calc. for C<sub>49</sub>H<sub>48</sub>IrNOP<sup>+</sup>: 890.3101 [M-BAr<sub>F</sub>]<sup>+</sup>; found: 890.3101.

[α]<sub>D</sub><sup>20</sup> = +42.0 (c = 0.46, CHCl<sub>3</sub>).

**Iridium complex ((S)-2.71)**

The reaction was set up as described in the general procedure **GP5** except using the pyridyl alcohol (**S**)-**2.58** (60.0 mg, 230  $\mu\text{mol}$ , 1.00 eq.), 4-dimethylaminopyridine (35.0 mg, 276  $\mu\text{mol}$ , 1.20 eq.) and chloro-di-(2-methylphenyl)-phosphine (70.0 mg, 276  $\mu\text{mol}$ , 1.20 eq.) in abs.  $\text{CH}_2\text{Cl}_2$  (1.4 mL). This solution was filtered into  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (77.0 mg, 115  $\mu\text{mol}$ , 0.50 eq.) and  $\text{NaBAr}_\text{F}$  (246 mg, 276  $\mu\text{mol}$ , 1.20 eq.). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 16$  cm, pentane: $\text{Et}_2\text{O}$  (2:1)  $\rightarrow$   $\text{CH}_2\text{Cl}_2$ ) afforded the product (154 mg, 128  $\mu\text{mol}$ , 56%) as an orange solid.

$\text{C}_{69}\text{H}_{50}\text{BF}_2\text{IrNOP}$  (1637.12 g/mol):

**MP**: 73-76  $^\circ\text{C}$ .

**TLC**:  $R_f = 0.95$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 7.67 (s, 1H, ar-*H*), 7.63 (s, 8H, ar-*H*), 7.52 (ddd,  $J$  = 15.0, 8.6, 6.4 Hz, 1H, ar-*H*), 7.46 (s, 5H, ar-*H*), 7.31-7.21 (m, 4H, ar-*H*), 7.16-7.09 (m, 2H, ar-*H*), 7.04 (q,  $J$  = 9.3 Hz, 3H, ar-*H*), 6.76-6.60 (m, 1H, ar-*H*), 6.33-6.13 (m, 1H, ar-*H*), 4.46-4.29 (m, 1H), 3.35-3.17 (m, 1H), 2.97-2.72 (m, 3H), 2.66 (s, 3H), 2.61-2.49 (m, 1H), 2.36-2.25 (m, 1H), 2.25-2.11 (s, 4H), 2.01-1.76 (m, 5H), 1.74-1.57 (m, 1H), 1.35-1.17 (m, 4H).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 162.2 (q,  $J$  = 50 Hz,  $\text{BAr}_\text{F}$ ), 155.9 (s, ar-C), 150.0 (s, ar-C), 142.2-141.9 (m), 141.5 (s, ar-C), 141.4-141.1 (m, ar-C), 138.0 (s,  $\text{BAr}_\text{F}$ ), 135.2 (s, ar-C), 133.7 (t,  $J$  = 10 Hz, ar-C), 133.4 (s, ar-C), 132.9 (s, ar-C), 132.6-132.0 (m, ar-C), 131.1 (d,  $J$  = 13.0 Hz), 131.1 (s, ar-C), 129.3 (qq,  $J_{\text{CF}}$  = 33 Hz, 3 Hz,  $\text{BAr}_\text{F}$ ), 126.8 (d,  $J$  = 11 Hz), 126.3 (s, ar-C), 126.1 (s, ar-C), 123.6 (s, ar-C), 120.9 (s, ar-C), 117.8 (sept,  $J_{\text{CF}}$  = 4 Hz,  $\text{BAr}_\text{F}$ ), 112.9-112.0 (m), 97.4 (s, CH COD), 76.3 (s, COP), 68.2 (s, CH), 37.3 (d,  $J$  = 3 Hz,  $\text{CH}_2$  COD), 35.3 (s,  $\text{CH}_2$ ), 30.8 (d,  $J$  = 10 Hz,  $\text{CH}_2$  COD), 29.1 (s,  $\text{CH}_2$ ), 28.1 (s,  $\text{CH}_2$ ), 24.6 (d,  $J$  = 3 Hz,  $\text{CH}_2$  COD), 22.5 (d,  $J$  = 5 Hz, CH COD), 17.8 (s,  $\text{CH}_2$ ).

**$^{31}\text{P}\{^1\text{H}\}$  NMR** (161 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 100.8 (br s).

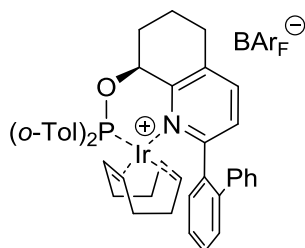
**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = -62.8 (s), -108.5 (s), -114.6 (s).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2926 (w), 1628 (w), 1610 (w), 1469 (m), 1353 (m), 1272 (s), 1115 (s), 1005 (m), 965 (w), 931 (w), 886 (w), 861 (w), 753 (m), 730 (m), 712 (m).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $C_{37}H_{38}IrNOP^+$ : 774.2285  $[M-BAr_F]^+$ ; found: 774.2281.

$[\alpha]_D^{20} = +25.2$  ( $c = 0.30$ ,  $CHCl_3$ ).

### Iridium complex ((*S*)-2.67)



The reaction was set up as described in the general procedure **GP5** except using the pyridyl alcohol (**S**)-2.56 (30.0 mg, 100  $\mu$ mol, 1.00 eq.), 4-dimethylaminopyridine (12.5 mg, 100  $\mu$ mol, 1.20 eq.) and chloro-di-(2-methylphenyl)-phosphine (25.0 mg, 100  $\mu$ mol, 1.00 eq.) in abs.  $CH_2Cl_2$  (1.4 mL). This solution was filtered into  $[Ir(COD)Cl]_2$  (27.5 mg, 50.0  $\mu$ mol, 0.50 eq.) and  $NaBAr_F$  (246 mg, 276  $\mu$ mol, 1.20 eq.). Column chromatography ( $SiO_2$ ,  $d \times h$ : 3  $\times$  16 cm,  $CH_2Cl_2$ ) afforded the product (111 mg, 65  $\mu$ mol, 65%) as an orange solid.

$C_{75}H_{56}BF_{24}IrNOP$  (1677.24 g/mol).

**MP**: 89-92 °C.

**TLC**:  $R_f = 0.96$  ( $SiO_2$ ,  $CH_2Cl_2$ , UV).

**$^1H$  NMR** (400 MHz,  $CD_2Cl_2$ )  $\delta$  = 8.00-7.87 (m, 1H, ar-*H*), 7.83 (td,  $J = 7.6, 1.4$  Hz, 1H, ar-*H*), 7.79 (t,  $J = 2.9$  Hz, 8H,  $BAr_F$ ), 7.71 (t,  $J = 7.4$  Hz, 1H, ar-*H*), 7.66 (dd,  $J = 7.8, 1.2$  Hz, 1H, ar-*H*), 7.61 (s, 4H,  $BAr_F$ ), 7.48 (t,  $J = 4.8$  Hz, 2H, ar-*H*), 7.42-7.36 (m, 2H, ar-*H*), 7.36-7.25 (m, 5H, ar-*H*), 7.25-7.18 (m, 1H, ar-*H*), 7.10-7.02 (m, 2H, ar-*H*), 6.84 (s, 1H, ar-*H*), 6.76 (d,  $J = 8.2$  Hz, 1H, ar-*H*), 6.50 (ddd,  $J = 6.9, 4.5, 2.4$  Hz, 1H, ar-*H*), 5.36 (t,  $J = 1.0$  Hz, 2H), 5.26 (s, 1H), 3.50 (q,  $J = 7.7$  Hz, 1H), 3.09-2.90 (m, 4H), 2.90-2.77 (m, 1H, *CH*), 2.77-2.68 (m, 1H, *CH*), 2.70-2.45 (m, 4H,  $CH_2$ ), 2.43-2.29 (m, 1H, *CH*), 2.25-1.92 (m, 6H,  $CH_3$ ), 1.50-1.37 (m, 1H, *CH*), 1.38-1.25 (m, 2H,  $CH_2$ ), 1.26-1.14 (m, 1H, *CH*).

**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CD_2Cl_2$ )  $\delta$  (ppm) = 161.0 (q,  $J = 50.1$  Hz,  $BAr_F$ ), 158.5 (s, ar-*C*), 153.0 (s, ar-*C*), 141.0-140.9 (m, ar-*C*), 139.3 (s, ar-*C*), 138.6 (s, ar-*C*), 137.9 (s, ar-*C*), 136.3 (s, ar-*C*), 134.9 (s,  $BAr_F$ ), 134.0 (s, ar-*C*), 133.3 (s, ar-*C*), 132.8 (s, ar-*C*), 131.8 (s, ar-*C*), 131.3-131.6 (m, ar-*C*), 131.0 (s, ar-*C*), 130.9 (s, ar-*C*), 130.7 (s, ar-*C*), 128.3-128.2 (m, ar-*C*),

129.4 (s, ar-C), 128.7 (s, ar-C), 127.9 (s, ar-C), 127.6 (s, ar-C), 126.0 (s, ar-C), 125.5 (s, ar-C), 126.1 (q,  $J = 272$  Hz, BAr<sub>F</sub>), 119.8 (s, ar-C), 116.7 (sept,  $J = 3$  Hz, BAr<sub>F</sub>), 75.4, 68.3, 53.1, 53.0, 52.8, 52.6, 35.4, 33.8, 29.5 (d,  $J_{CP} = 10$  Hz), 27.7, 27.4 (s), 23.4 (d,  $J_{CP} = 3$  Hz), 21.2 (d,  $J = 5$  Hz), 17.2.

**<sup>31</sup>P{<sup>1</sup>H} NMR** (161 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$ /ppm = 98.7 (s).

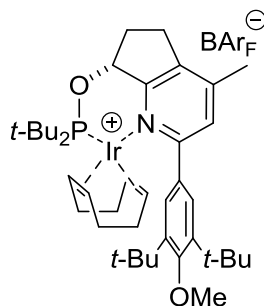
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 2958$  (w), 1352 (m), 1272 (s), 1116 (s), 860 (w), 744 (m), 711 (m), 701 (m).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for C<sub>49</sub>H<sub>44</sub>IrNOP<sup>+</sup>: 814.2787 [M-BAr<sub>F</sub>]<sup>+</sup>; found: 814.2794.

**$[\alpha]_D^{20}$**  = +45.0 (c = 0.17, CHCl<sub>3</sub>).

## General procedure: Synthesis of di-*tert*-butyllphosphinite based catalyst GP6

### Iridium complex (R)-(2.63)



The analogous (*R*)-pyridine alcohol (50 mg, 136  $\mu\text{mol}$ , 1.00 eq.) was added to a dry Young tube which was evacuated and backfilled with argon three times. KH (8.2 mg, 189  $\mu\text{mol}$ , 1.50 eq.) and di-*tert*-butylchlorophosphine (24.5 mg, 136  $\mu\text{mol}$ , 1.00 eq.) were added and rinsed down with DMF (0.45 mL). The increasingly dark solution was stirred for 120 h at room temperature. DMF was completely evaporated in HV in a 60 °C hot water bath to assist complete removal of solvent. The brown residue was taken up in toluene (2 mL) and filtered through a plug of celite (2  $\times$  2 cm). Toluene was evaporated in HV and the resulting violet residue was taken up in abs.  $\text{CH}_2\text{Cl}_2$  (2 mL).  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (46 mg, 136  $\mu\text{mol}$ , 1.00 eq.) was added and the solution was stirred for 1 h at room temperature.  $\text{NaBArF}$  (142 mg, 163  $\mu\text{mol}$ , 1.20 eq.) was added and the brownish solution was stirred for 14 h at room temperature. The solution was adsorbed and concentrated onto silica (2 g). Purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 3  $\times$  20 cm, hexane: $\text{CH}_2\text{Cl}_2$  (1:1)) afforded the complex (117 mg, 70  $\mu\text{mol}$ , 51%) as a red solid.

$\text{C}_{72}\text{H}_{74}\text{BF}_{24}\text{IrNO}_2\text{P}$  (1675.35 g/mol):

**MP:** 142-143 °C.

**TLC:**  $R_f$  = 0.39 ( $\text{SiO}_2$ , hexane: $\text{CH}_2\text{Cl}_2$  (1:1), UV).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 7.71 (s, 8H,  $\text{BArF}$ ), 7.66 (s, 2H, ar-*H*), 7.54 (s, 4H,  $\text{BArF}$ ), 7.34 (s, 1H, ar-*H*), 5.70-5.60 (m, 1H, *CH* COD), 5.23-5.19 (m, 1H, *HCOP*), 4.67-4.75 (m, 1H, *CH* COD), 4.05-4.00 (m, 1H, *CH* COD), 3.80 (s, 3H,  $\text{OCH}_3$ ), 3.06-3.00 (m, 1H,  $\text{CH}_2$ ), 2.90-2.74 (m, 3H, *CH* COD and  $\text{CH}_2$ ), 2.38 (s, 3H,  $\text{CH}_3$ ), 2.38-2.32 (m, 1H,  $\text{CH}_2$  COD), 2.14-1.93 (m, 3H,  $\text{CH}_2$  COD and  $\text{CH}_2$ ), 1.83 (dd,  $J$  = 15.0, 7.6 Hz, 1H,  $\text{CH}_2$  COD), 1.53-1.45 (m, 1H,  $\text{CH}_2$  COD), 1.48 (s, 18H, 2  $\times$   $\text{C}(\text{CH}_3)_3$ ), 1.47 (d,  $J_{\text{HP}}$  = 14.5 Hz, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.29-1.21



(m, 1H, CH<sub>2</sub> COD), 1.18-1.09 (m, 1H, CH<sub>2</sub> COD), 1.10 (d,  $J_{HP}$  = 14.5 Hz, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 0.95-0.89 (m, 1H, CH<sub>2</sub> COD).

<sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = 162.3 (q,  $J_{BC}$  = 50 Hz, BAr<sub>F</sub>), 162.3 (s, ar-C), 159.5 (d,  $J_{CP}$  = 2 Hz, ar-C), 149.9 (s, ar-C), 145.6 (s, ar-C), 138.1 (s, ar-C), 135.4 (s, BAr<sub>F</sub>), 135.0 (s, ar-C), 132.0 (s, ar-C), 129.5 (qq,  $J_{CF}$  = 32 Hz,  $J_{BC}$  = 3 Hz, BAr<sub>F</sub>), 127.5 (s, ar-C), 127.5 (s, ar-C), 125.1 (q,  $J_{CF}$  = 268 Hz, BAr<sub>F</sub> CF<sub>3</sub>), 118.1 (sept, BAr<sub>F</sub>), 91.1 (d,  $J_{CP}$  = 5 Hz, CH COD), 85.2 (d,  $J_{CP}$  = 2 Hz, COP), 78.6 (d,  $J_{CP}$  = 19 Hz, CH COD), 75.1 (s, CH COD), 64.9 (s, OCH<sub>3</sub>), 61.3 (s, CH COD), 41.7 (d,  $J_{CP}$  = 19 Hz, C(CH<sub>3</sub>)<sub>3</sub>), 40.3 (d,  $J_{CP}$  = 21 Hz, C(CH<sub>3</sub>)<sub>3</sub>), 38.4 (d,  $J_{CP}$  = 4 Hz, CH<sub>2</sub> COD), 36.8 (s, C(CH<sub>3</sub>)<sub>3</sub>), 35.6 (s, CH<sub>2</sub> COD), 32.4 (s, C(CH<sub>3</sub>)<sub>3</sub>), 30.0 (d,  $J_{CP}$  = 8 Hz, CH<sub>2</sub>), 29.1 (d,  $J_{CP}$  = 7 Hz, C(CH<sub>3</sub>)<sub>3</sub>), 28.6 (s, CH<sub>2</sub> COD), 26.9 (s, CH<sub>2</sub>), 24.2 (d,  $J_{CP}$  = 4 Hz, CH<sub>2</sub> COD), 19.2 (s, CH<sub>3</sub>).

<sup>31</sup>P{<sup>1</sup>H} NMR (161 MHz, CDCl<sub>3</sub>): δ/ppm = 143.7 (s).

<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>): δ/ppm = -63.1 (s).

<sup>11</sup>B{<sup>1</sup>H} NMR (160 MHz, CDCl<sub>3</sub>): δ/ppm = -5.6 (s).

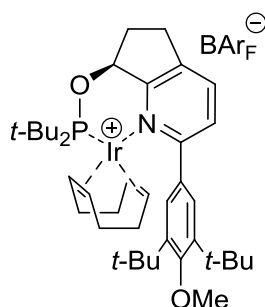
IR (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2963 (m), 2881 (w), 1609 (w), 1458 (w), 1353 (m), 1273 (s), 1158 (m), 1200 (s), 1007 (w), 885 (m), 836 (m), 809 (m), 712 (m), 671 (m).

MS (FAB NBA):  $m/z$  (%): 812.4 (100), 698.3 (17), 350.2 (10).

EA (C<sub>72</sub>H<sub>74</sub>BF<sub>24</sub>IrNO<sub>2</sub>P): calc.: C 51.62, H 4.45, N 0.84; found: C 51.67, H 4.46, N 1.00.

$[\alpha]_D^{20}$  = +10.5 (c = 0.53, CHCl<sub>3</sub>).

### Iridium complex (S)-2.78



The reaction was set up as described in the general procedure **GP6** except using the pyridyl alcohol (S)-**2.50** (120 mg, 342  $\mu\text{mol}$ , 1.00 eq.), KH (20.6 mg, 512  $\mu\text{mol}$ , 1.50 eq.) and di-*tert*-butylchlorophosphine (74.0  $\mu\text{L}$ , 342  $\mu\text{mol}$ , 1.00 eq.) in DMF (0.5 mL). This solution was stirred for 14 h and filtered into [Ir(COD)Cl]<sub>2</sub> (116 mg, 171  $\mu\text{mol}$ , 0.50 eq.) and NaBAr<sub>F</sub> (357 mg, 365  $\mu\text{mol}$ , 1.20 eq.). Column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3.5  $\times$  20 cm,

pentane:Et<sub>2</sub>O (3:1) → pentane:Et<sub>2</sub>O (1:1)) afforded the complex (370 mg, 223 μmol, 65%) as a red solid.

C<sub>73</sub>H<sub>78</sub>BF<sub>24</sub>IrNO<sub>2</sub>P (1661.47 g/mol).

**MP:** 186-190 °C.

**TLC:** R<sub>f</sub> = 0.15 (SiO<sub>2</sub>, pentane:CH<sub>2</sub>Cl<sub>2</sub> (3:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ = 7.73 (d, *J* = 8.0 Hz, 1H, ar-*H*), 7.64 (s, 9H, BAr<sub>F</sub>, ar-*H*), 7.47 (s, 5H, BAr<sub>F</sub>, ar-*H*), 7.45 (s, 1H, ar-*H*), 5.73-5.47 (m, 1H), 5.19 (t, *J* = 7.1, 1H, COH), 4.65-4.52 (m, 1H), 4.08-3.90 (m, 1H), 3.73 (s, 3H, OCH<sub>3</sub>), 3.00-3.08 (m, 1H), 2.95-2.63 (m, 3H), 2.36-2.22 (m, 1H), 2.12-1.86 (m, 3H), 1.85-1.73 (m, 1H), 1.47-1.32 (m, 27H), 1.29-1.14 (m, 2H), 1.03 (d, *J* = 14.6 Hz, 9H), 0.93-0.84 (m, 1H), 0.84-0.80 (m, 1H).

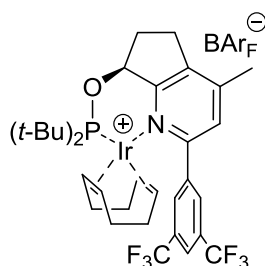
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = 162.4 (q, *J* = 50 Hz, BAr<sub>F</sub>), 162.4 (s, ar-C), 162.2 (s, ar-C), 160.3 (s, ar-C), 145.6 (s, ar-C), 138.5 (s, ar-C), 137.1 (s, ar-C), 135.2 (s, BAr<sub>F</sub>), 134.6 (s, ar-C), 131.2 (s, ar-C), 129.2 (qq, *J* = 32, 4 Hz, BAr<sub>F</sub>), 124.5 (q, *J* = 279 Hz, BAr<sub>F</sub>), 120.9 (s, ar-C), 117.8 (sept, *J*<sub>CF</sub> = 4 Hz, BAr<sub>F</sub>), 91.0 (d, *J*<sub>CP</sub> = 5 Hz), 84.6 (d, *J*<sub>CP</sub> = 2 Hz), 78.5 (d, *J*<sub>CP</sub> = 19 Hz), 75.5, 64.7, 61.5, 54.0, 53.7, 41.5 (d, *J*<sub>CP</sub> = 19 Hz), 40.2 (d, *J*<sub>CP</sub> = 20 Hz), 38.2 (d, *J*<sub>CP</sub> = 4 Hz), 35.4, 32.2, 30.2 (d, *J*<sub>CP</sub> = 8 Hz), 28.9 (d, *J*<sub>CP</sub> = 7 Hz), 28.3 (d, *J*<sub>CP</sub> = 2 Hz), 27.9, 24.0 (d, *J*<sub>CP</sub> = 4 Hz).

**<sup>31</sup>P{<sup>1</sup>H} NMR** (161 MHz, CDCl<sub>3</sub>): δ/ppm = 142.2 (s).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2964 (w), 1394 (m), 1307 (s), 1225 (s), 1158 (s), 924 (m), 696 (m), 682 (m), 669 (m).

**HRMS** (ESI, 4500 V, 180 °C):: (*m/z*) calc. for C<sub>39</sub>H<sub>60</sub>IrNO<sub>2</sub>P<sup>+</sup>: 798.3988 [M-BAr<sub>F</sub>]<sup>+</sup>; found: 798.3997.

**[α]<sub>D</sub><sup>20</sup>** = -13.2 (c = 0.54, CHCl<sub>3</sub>).

**Iridium complex ((S)-2.64)**

The reaction was set up as described in the general procedure **GP6** except using the analogous pyridyl alcohol (30 mg, 83.5  $\mu$ mol, 1.00 eq.), KH (5.0 mg, 125  $\mu$ mol, 1.50 eq.) and di-*tert*-butylchlorophosphine (14.2 mg, 83.5  $\mu$ mol, 1.00 eq.) in DMF (0.45 mL). This solution was stirred for 120 h and filtered into [Ir(COD)<sub>2</sub>]<sub>2</sub>BArF<sub>4</sub> (105 mg, 83.5  $\mu$ mol, 1.20 eq.). Column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3  $\times$  20 cm, hexane:CH<sub>2</sub>Cl<sub>2</sub> (1:1)) and recrystallization from a mixture of Et<sub>2</sub>O and hexane afforded the complex (40 mg, 24  $\mu$ mol, 29%) in 95% purity determined by <sup>31</sup>P NMR.

C<sub>65</sub>H<sub>54</sub>BF<sub>30</sub>IrNOP (1669.11 g/mol).

**MP:** 78-80 °C.

**TLC:** R<sub>f</sub> = 0.68 (SiO<sub>2</sub>, pentane:CH<sub>2</sub>Cl<sub>2</sub> (1:1), UV).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 8.58 (s, 2H, ar-*H*), 8.21 (s, 1H, ar-*H*), 7.70 (s, 8H, BArF<sub>4</sub>), 7.50 (s, 5H, ar-*H* and BArF<sub>4</sub>), 5.73-5.68 (m, 1H, CH COD), 5.40-5.35 (m, 1H, CHOP), 4.47 (s, 1H, CH COD), 4.16 (s, 1H, CH COD), 3.04-2.98 (m, 1H, CH<sub>2</sub>), 2.84-2.78 (m, 1H, CH<sub>2</sub> COD), 2.43-2.31 (m, 2H, CH COD and CH<sub>2</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 2.08-2.03 (m, 2H, CH<sub>2</sub> COD), 1.88-1.80 (m, 2H, CH<sub>2</sub> COD), 1.49 (d,  $J_{\text{HP}}$  = 13.8 Hz, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.39-1.33 (m, 2H, CH<sub>2</sub>), 1.18-1.12 (s, 1H, CH<sub>2</sub> COD), 1.08 (d,  $J_{\text{HP}}$  = 14.7 Hz, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 0.84-0.82 (m, 1H, CH<sub>2</sub> COD).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 161.8 (q,  $J_{\text{BC}}$  = 50 Hz, BArF<sub>4</sub>), 160.9 (s, ar-C), 156.7 (s, ar-C), 150.9 (s, ar-C), 141.0 (s, ar-C), 139.7 (s, ar-C), 134.9 (s, BArF<sub>4</sub>), 133.1 (q,  $J_{\text{CF}}$  = 33 Hz, ar-C), 130.7 (s, ar-C), 129.0 (qq,  $J_{\text{CF}}$  = 31 Hz,  $J_{\text{BC}}$  = 3 Hz, BArF<sub>4</sub>), 127.6 (d,  $J_{\text{CP}}$  = 3 Hz), 124.7 (q,  $J_{\text{CF}}$  = 273 Hz, BArF<sub>4</sub>), 124.7 (sept,  $J_{\text{CF}}$  = 4 Hz, ar-C), 124.7 (s, ar-C), 122.6 (q,  $J_{\text{CF}}$  = 279 Hz, ar-C), 117.6 (sept,  $J_{\text{CF}}$  = 4 Hz, BArF<sub>4</sub>), 91.5 (d,  $J_{\text{CP}}$  = 5 Hz, CH COD), 91.44 (s, CH COD), 84.8 (d,  $J_{\text{CP}}$  = 2 Hz, CH COD), 78.9 (d,  $J_{\text{CP}}$  = 2 Hz, CH COD), 76.3 (s, COP), 63.0 (s, CH COD), 41.1 (d,  $J_{\text{CP}}$  = 19 Hz, C(CH<sub>3</sub>)<sub>3</sub>), 40.1 (d,  $J_{\text{CP}}$  = 21 Hz, C(CH<sub>3</sub>)<sub>3</sub>), 37.3 (d,  $J_{\text{CP}}$  = 3 Hz, CH<sub>2</sub> COD), 31.7 (s, CH<sub>2</sub> COD), 29.4 (d,  $J_{\text{CP}}$  = 8 Hz, CH<sub>2</sub> COD), 28.5 (s, C(CH<sub>3</sub>)<sub>3</sub>), 28.5 (s, C(CH<sub>3</sub>)<sub>3</sub>), 27.9 (s, CH<sub>2</sub>), 26.3 (s, CH<sub>2</sub>), 23.9 (d,  $J_{\text{CP}}$  = 8 Hz, CH<sub>2</sub> COD), 18. (s, CH<sub>3</sub>).

**<sup>31</sup>P{<sup>1</sup>H} NMR** (161 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 144.6 (s).<sup>[1]</sup>

$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = -62.6$  (s, 24F,  $\text{BAr}_\text{F}$ ,  $\text{CF}_3$ ),  $-62.7$  (s, 6F,  $\text{CF}_3$ ).

$^{11}\text{B}\{^1\text{H}\}$  NMR (160 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = -5.6$  (s).

IR (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 2964$  (w), 2930 (w), 2891 (w), 1609 (m), 1457 (w), 1394 (w), 1353 (s), 1272 (s), 1114 (s), 882 (m), 838 (m), 710 (m).

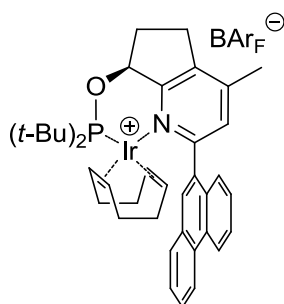
MS (FAB NBA):  $m/z$  (%): 806.2 (100)  $[\text{M-BAr}_\text{F}]^+$ , 696.1 (17), 640.1 (33), 344.0 (12).

EA ( $\text{C}_{65}\text{H}_{54}\text{BF}_{30}\text{IrNOP}$ ): calc.: C 46.78, H 3.26, N 0.84; found: C 46.22, H 3.45, N 0.90.

$[\alpha]_\text{D}^{20} = -39.1$  ( $c = 0.32$ ,  $\text{CHCl}_3$ ).

[I] = Impurity at  $-131.6$  ppm.

### Iridium complex ((*S*)-2.69)



The reaction was set up as described in the general procedure **GP6** except using the pyridyl alcohol (*S*)-**2.57** (40 mg, 123  $\mu\text{mol}$ , 1.00 eq.), KH (7.4 mg, 123  $\mu\text{mol}$ , 1.50 eq.) and di-*tert*-butylchlorophosphine (23.4  $\mu\text{L}$ , 123  $\mu\text{mol}$ , 1.00 eq.) in DMF (0.4 mL). This solution stirred for 63 h and was filtered into  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (41 mg, 61  $\mu\text{mol}$ , 0.50 eq.) and  $\text{NaBAr}_\text{F}$  (131 mg, 147  $\mu\text{mol}$ , 1.20 eq.). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 25$  cm,  $\text{CH}_2\text{Cl}_2$ ) afforded the complex (20 mg, 12  $\mu\text{mol}$ , 10%) as a red solid.

$\text{C}_{71}\text{H}_{60}\text{BF}_{24}\text{IrNOP}$  (1633.23 g/mol):

MP: 192-193  $^\circ\text{C}$ .

TLC:  $R_f = 0.78$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , UV).

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm} = 8.91$  (d,  $J = 8.3$  Hz, 1H), 8.86 (d,  $J = 8.3$  Hz, 1H), 8.73 (s, 1H), 7.99 (d,  $J = 7.8$  Hz, 1H), 7.93-7.76 (m, 4H), 7.72 (s, 8H), 7.66 (s, 1H), 7.62 (s, 1H), 7.56 (s, 4H), 5.68-5.62 (m, 1H), 5.16-5.10 (m, 1H), 4.81-4.74 (m, 1H), 4.10-4.01 (m, 1H), 3.24-3.11 (m, 1H), 3.06-3.00 (m, 1H), 2.89-2.74 (m, 1H), 2.57-2.45 (m, 4H), 2.18-1.94 (m, 3H), 1.53 (d,  $J = 13.7$  Hz, 9H), 1.40 (q,  $J = 7.4$  Hz, 1H), 1.18 (d,  $J = 14.4$  Hz, 9H), 1.12-1.05 (m, 1H), 1.04-0.97 (m, 1H), 0.78-0.62 (m, 2H),  $-0.02$ – $-0.15$  (m, 1H).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 162.3 (q,  $J_{\text{CB}}$  = 50 Hz,  $\text{BAr}_\text{F}$ ), 160.4 (d,  $J_{\text{CP}}$  = 3 Hz, ar-C), 157.9 (s, ar-C), 149.3 (s, ar-C), 139.3 (s, ar-C), 136.0 (s, ar-C), 135.3 (s,  $\text{BAr}_\text{F}$ ), 133.0 (s, ar-C), 131.6 (s, ar-C), 131.6 (s, ar-C), 130.9 (s, ar-C), 130.2 (s, ar-C), 129.5 (s, ar-C), 129.4 (qq,  $J_{\text{CF}}$  = 32 Hz, 3 Hz,  $\text{BAr}_\text{F}$ ), 129.0 (s, ar-C), 128.8 (s, ar-C), 128.7 (s, ar-C), 128.6 (s, ar-C), 126.2 (s, ar-C), 126.0 (s, ar-C), 125.1 (q,  $J_{\text{CF}}$  = 274 Hz,  $\text{BAr}_\text{F}$ ), 124.2 (s, ar-C), 123.8 (s, ar-C), 118.0 (sept,  $J_{\text{CF}}$  = 3 Hz,  $\text{BAr}_\text{F}$ ), 89.0 (d,  $J_{\text{CP}}$  = 5 Hz, CH COD), 85.2 (d,  $J_{\text{CP}}$  = 2 Hz, CH COD), 76.9 (s, COP), 76.6 (d,  $J_{\text{CP}}$  = 20 Hz, CH COD), 62.2 (s, CH COD), 42.0 (d,  $J_{\text{CP}}$  = 18 Hz,  $\text{C}(\text{CH}_3)_3$ ), 40.2 (d,  $J_{\text{CP}}$  = 21 Hz,  $\text{C}(\text{CH}_3)_3$ ), 36.6 (d,  $J_{\text{CP}}$  = 4 Hz,  $\text{CH}_2$  COD), 36.1 (s,  $\text{CH}_2$ ), 29.8 (d,  $J_{\text{CP}}$  = 8 Hz,  $\text{CH}_2$  COD), 29.2 (s,  $\text{C}(\text{CH}_3)_3$ ), 29.1 (s,  $\text{C}(\text{CH}_3)_3$ ), 28.4 (s,  $\text{CH}_2$  COD), 27.7 (s,  $\text{CH}_2$ ), 23.3 (d,  $J_{\text{CP}}$  = 4 Hz,  $\text{CH}_2$  COD), 19.4 (s,  $\text{CH}_3$ ).

**$^{31}\text{P}\{^1\text{H}\}$  NMR** (161 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 142.6 (s).

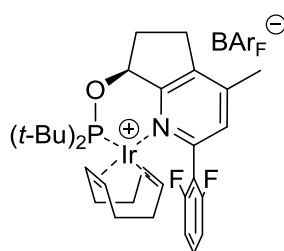
**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = -62.9 (s).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2965 (w), 2931 (w), 2170 (w), 2055 (w), 1612 (w), 1470 (w), 1354 (s), 1274 (s), 1118 (s), 1001 (w), 961 (w), 886 (m), 839 (m), 808 (w), 746 (w), 713 (m), 681 (m), 616 (w).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{39}\text{H}_{48}\text{IrNOP}^+$ : 770.3099 [ $\text{M}-\text{BAr}_\text{F}$ ] $^+$ ; found: 707.3102.

$[\alpha]_\text{D}^{20}$  = -71 ( $c$  = 0.21,  $\text{CHCl}_3$ ).

### Iridium complex ((*S*)-2.70)



The reaction was set up as described in the general procedure **GP6** except using the pyridyl alcohol (*S*)-**2.58** (40 mg, 123  $\mu\text{mol}$ , 1.00 eq.), KH (9.2 mg, 230  $\mu\text{mol}$ , 1.50 eq.) and di-*tert*-butylchlorophosphine 30  $\mu\text{L}$ , 153  $\mu\text{mol}$ , 1.00 eq.) in DMF (0.5 mL). This solution was stirred for 14 h, and filtered into  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (51 mg, 77  $\mu\text{mol}$ , 0.50 eq.) and  $\text{NaBAr}_\text{F}$  (163 mg, 184  $\mu\text{mol}$ , 1.20 eq.). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ : 3  $\times$  16 cm, pentane: $\text{Et}_2\text{O}$  (2:1)  $\rightarrow$   $\text{CH}_2\text{Cl}_2$ ) afforded the complex (91 mg, 58  $\mu\text{mol}$ , 38%) as a red solid.

$\text{C}_{66}\text{H}_{54}\text{BF}_2\text{IrNOP}$  (1569.26 g/mol):

**MP:** 177-178 °C.

**TLC:**  $R_f$  = 0.89 (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, UV).

**<sup>1</sup>H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ /ppm = 7.74 (s, 8H), 7.69-7.58 (m, 1H), 7.57 (s, 4H), 7.41 (s, 1H), 7.21 (dt,  $J$  = 29.6, 9.0 Hz, 2H), 5.60 (ddd,  $J$  = 7.7, 5.4, 2.1 Hz, 1H), 5.52-5.43 (m, 1H), 5.06-4.95 (m, 1H), 4.11 (tt,  $J$  = 8.4, 5.1 Hz, 1H), 3.12 (ddd,  $J$  = 16.3, 9.2, 6.6 Hz, 1H), 2.96 (ddd,  $J$  = 17.4, 9.5, 3.6 Hz, 1H), 2.80-2.59 (m, 2H), 2.56-2.45 (m, 1H), 2.43 (s, 3H), 2.22-2.09 (m, 1H), 2.09-1.93 (m, 2H), 1.86-1.75 (m, 1H), 1.51 (d,  $J$  = 13.6 Hz, 9H), 1.3-1.11 (m, 3H), 0.91 (d,  $J$  = 14.7 Hz, 9H), 0.86-0.71 (m, 1H).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ /ppm = 162.4 (q,  $J_{CB}$  = 50 Hz, BAr<sub>F</sub>), 161.4 (d,  $J_{CP}$  = 3 Hz, ar-C), 150.4 (s, ar-C), 149.9 (s, ar-C), 140.3 (s, ar-C), 135.4 (s, BAr<sub>F</sub>), 133.9 (s, ar-C), 133.5 (t,  $J_{CF}$  = 10 Hz, ar-C), 129.5 (qq,  $J_{CF}$  = 32 Hz, 3 Hz, BAr<sub>F</sub>), 125.2 (q,  $J_{CF}$  = 274 Hz, BAr<sub>F</sub>), 118.1 (sept,  $J_{CF}$  = 4 Hz, BAr<sub>F</sub>), 117.4 (t,  $J_{CF}$  = 18 Hz, ar-C), 113.3-112.7 (m, ar-C), 89.7 (d,  $J_{CP}$  = 4 Hz, CH COD), 85.5 (d,  $J_{CP}$  = 2 Hz, CH COD), 78.1 (s, COP), 74.7 (d,  $J_{CP}$  = 21 Hz, CH COD), 60.6 (s, CH COD), 41.5 (d,  $J_{CP}$  = 17 Hz, C(CH<sub>3</sub>)<sub>3</sub>), 39.9 (d,  $J_{CP}$  = 20 Hz, C(CH<sub>3</sub>)<sub>3</sub>), 38.2 (d,  $J_{CP}$  = 5 Hz, CH<sub>2</sub> COD), 36.6 (s, CH<sub>2</sub>), 29.8 (d,  $J_{CP}$  = 8 Hz, CH<sub>2</sub> COD), 28.8 (s, C(CH<sub>3</sub>)<sub>3</sub>), 28.4-28.2 (m, C(CH<sub>3</sub>)<sub>3</sub>, CH<sub>2</sub> COD), 27.7 (s, CH<sub>2</sub>), 24.5 (d,  $J_{CP}$  = 4 Hz, CH COD), 19.2 (s, CH<sub>3</sub>).

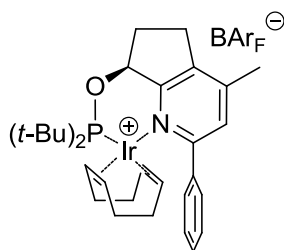
**<sup>31</sup>P{<sup>1</sup>H} NMR** (161 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 142.0 (s).

**<sup>19</sup>F{<sup>1</sup>H} NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = -62.8 (s), -105.0 (s), -109.4 (s).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 2960 (w), 2031 (w), 1611 (w), 1568 (w), 1470 (w), 1354 (m), 1273 (s), 1120 (s), 1048 (w), 1007 (m), 965 (w), 887 (m), 838 (m), 744 (w), 714 (m), 681 (m).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for C<sub>31</sub>H<sub>42</sub>F<sub>2</sub>IrNOP<sup>+</sup>: 706.2596 [M-BAr<sub>F</sub>]<sup>+</sup>; found: 706.2592.

**$[\alpha]_D^{20}$**  = -27 (c = 0.20, CHCl<sub>3</sub>).

**Iridium complex ((S)-2.79)**

The reaction was set up as described in the general procedure **GP6** except using the analogous (S)-pyridyl alcohol (21 mg, 91  $\mu\text{mol}$ , 1.00 eq.), KH (5.5 mg, 137  $\mu\text{mol}$ , 1.50 eq.) and di-*tert*-butylchlorophosphine (17  $\mu\text{L}$ , 91  $\mu\text{mol}$ , 1.00 eq.) in DMF (0.3 mL). This solution was stirred for 14 h and was filtered into  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (31 mg, 46  $\mu\text{mol}$ , 0.50 eq.) and  $\text{NaBAr}_\text{F}$  (97 mg, 109  $\mu\text{mol}$ , 1.20 eq.). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 15$  cm,  $\text{CH}_2\text{Cl}_2$ ) afforded the complex (60 mg, 39  $\mu\text{mol}$ , 43%) as a red solid.

$\text{C}_{63}\text{H}_{56}\text{BF}_{24}\text{IrNOP}$  (1533.11 g/mol):

**MP**: 169-170  $^\circ\text{C}$ .

**TLC**:  $R_f = 0.90$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 8.26 (d,  $J = 7.1$  Hz, 2H), 7.73 (s, 8H), 7.72-7.63 (m, 3H), 7.59 (s, 1H), 7.56 (s, 4H), 5.75 (s, 1H), 4.58-4.48 (m, 1H), 4.16-4.05 (m, 1H), 3.14-3.02 (m, 1H), 2.97-2.75 (m, 2H), 2.61-2.49 (m, 1H), 2.44 (s, 3H), 2.42-2.34 (m, 1H), 2.31-2.04 (m, 3H), 1.91-1.80 (m, 1H), 1.74-1.65 (m, 1H), 1.51 (d,  $J = 13.2$  Hz, 9H), 1.39-1.20 (m, 2H), 1.20-1.00 (m, 1H), 1.06 (d,  $J = 14.4$  Hz, 9H), 0.97-0.84 (m, 1H).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 162.3 (q,  $J_{\text{CB}} = 50$  Hz,  $\text{BAr}_\text{F}$ ), 160.4 (d,  $J_{\text{CP}} = 2$  Hz, ar-C), 160.0 (s, ar-C), 150.3 (s, ar-C), 139.3 (s, ar-C), 138.5 (s, ar-C), 135.4 (s,  $\text{BAr}_\text{F}$ ), 131.7 (s, ar-C), 130.4 (s, ar-C), 130.2 (s, ar-C), 129.4 (qq,  $J_{\text{CF}} = 32$  Hz, 3 Hz,  $\text{BAr}_\text{F}$ ), 128.1 (s, ar-C), 125.1 (q,  $J_{\text{CF}} = 273$  Hz,  $\text{BAr}_\text{F}$ ), 118.0 (sept,  $J_{\text{CF}} = 4$  Hz,  $\text{BAr}_\text{F}$ ), 91.0 (d,  $J_{\text{CP}} = 5$  Hz, CH COD), 85.8 (d,  $J_{\text{CP}} = 2$  Hz, CH COD), 79.6 (d,  $J_{\text{CP}} = 18$  Hz, CH COD), 74.0 (s, COP), 63.3 (s, CH COD), 41.8 (d,  $J_{\text{CP}} = 19$  Hz,  $\text{C}(\text{CH}_3)_3$ ), 40.3 (d,  $J_{\text{CP}} = 22$  Hz,  $\text{C}(\text{CH}_3)_3$ ), 37.7 (d,  $J_{\text{CP}} = 4$  Hz,  $\text{CH}_2$  COD), 35.7 (s,  $\text{CH}_2$ ), 29.9 (d,  $J_{\text{CP}} = 8$  Hz,  $\text{CH}_2$  COD), 28.9 (s,  $\text{C}(\text{CH}_3)_3$ ), 28.8 (s,  $\text{C}(\text{CH}_3)_3$ ), 28.3 (d,  $J_{\text{CP}} = 1$  Hz,  $\text{CH}_2$  COD), 27.1 (s,  $\text{CH}_2$ ), 24.3 (d,  $J_{\text{CP}} = 3$  Hz,  $\text{CH}_2$  COD), 19.3 (s,  $\text{CH}_3$ ).

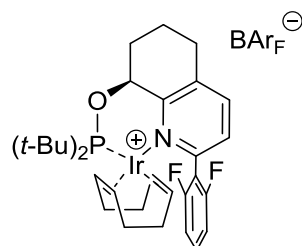
**$^{31}\text{P}\{^1\text{H}\}$  NMR** (161 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 142.1 (s).

**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = -62.8 (s).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2925 (w), 1723 (w), 1612 (w), 1464 (w), 1353 (m), 1272 (s), 1160 (m), 1120 (s), 1048 (w), 964 (w), 926 (w), 886 (m), 838 (w), 807 (w), 774 (w), 745 (w), 714 (m), 681 (m).

$[\alpha]_D^{20} = -40$  ( $c = 0.18$ ,  $\text{CHCl}_3$ ).

### Iridium complex ((S)-2.72)



The reaction was set up as described in the general procedure **GP6** except using the pyridyl alcohol (**S**)-**2.59** (60.0 mg, 230  $\mu\text{mol}$ , 1.00 eq.), KH (13.9 mg, 344  $\mu\text{mol}$ , 1.50 eq.) and di-*tert*-butylchlorophosphine in DMF:THF ((3:1), 3.0 mL). This solution was stirred for 14 h and filtered into a solution of  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (77.7 mg, 115  $\mu\text{mol}$ , 0.50 eq.) and  $\text{NaBArF}$  (257 mg, 276  $\mu\text{mol}$ , 1.20 eq.) in  $\text{CH}_2\text{Cl}_2$  (3 mL). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $3 \times 16$  cm, pentane: $\text{Et}_2\text{O}$  (2:1)  $\rightarrow$   $\text{CH}_2\text{Cl}_2$ ) afforded the complex (144 mg, 92  $\mu\text{mol}$ , 40%) as a red solid.

$\text{C}_{63}\text{H}_{54}\text{BF}_{26}\text{IrNOP}$  (1569.09 g/mol):

**MP**: 203-208  $^{\circ}\text{C}$ .

**TLC**:  $R_f = 0.85$  ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ , UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 7.67 (d,  $J = 8.3$  Hz, 1H, ar-*H*), 7.64 (s, 8H, ar-*H*), 7.55 (tt,  $J = 8.5$ , 6.3 Hz, 1H, ar-*H*), 7.47 (s, 4H,  $\text{BArF}$ ), 7.36 (dd,  $J = 8.0$ , 2.1 Hz, 1H, ar-*H*), 7.13 (dt,  $J = 24.0$ , 9.1 Hz, 2H, ar-*H*), 5.40 (dt,  $J = 8.8$ , 3.0 Hz, 1H), 5.38-5.29 (m, 1H), 5.24-5.20 (m, 2H), 5.02-4.09 (m, 1H), 4.14-3.95 (m, 1H), 2.96-2.78 (m, 1H), 2.76-2.61 (m, 2H), 2.48-2.37 (m, 1H), 2.01-1.89 (m, 3H), 1.89-1.82 (m, 2H), 1.79-1.62 (m, 1H), 1.61-1.50 (m, 1H), 1.42 (d,  $J = 13.5$  Hz, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.37-1.29 (m, 1H), 1.15-0.97 (m, 2H), 0.79 (d,  $J = 14.7$  Hz, 9H,  $\text{C}(\text{CH}_3)_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 162.7 (d,  $J_{\text{CP}} = 5$  Hz), 161.4 (q,  $J_{\text{CB}} = 50$  Hz), 156.0, 150.2, 140.4, 138.0, 135.2, 133.3 (t,  $J_{\text{CF}} = 10$  Hz), 132.4, 129.2 (qq,  $J_{\text{CF}} = 33$ , 3 Hz), 125.3, 128.6, 120.9 (s, ar-*C*), 117.7 (sept,  $J_{\text{CF}} = 4.1$  Hz), 112.9 (tt,  $J = 26$ , 4 Hz), 89.7 (d,  $J_{\text{CP}} = 3.8$  Hz), 78.2, 77.7, 74.9 (d,  $J_{\text{CP}} = 22$  Hz), 58.7, 41.1 (d,  $J_{\text{CP}} = 17$  Hz), 39.6 (d,  $J_{\text{CP}} = 20$  Hz),



38.0 (d,  $J_{CP} = 5$  Hz), 36.2, 30.6 (d,  $J_{CP} = 8$  Hz), 28.9, 28.7-27.8 (m), 28.1, 27.8 (t,  $J_{CP} = 7$  Hz), 24.2 (d,  $J = 4$  Hz), 17.1.

$^{31}\text{P}\{^1\text{H}\}$  NMR (161 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 136.3$  (s).

$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm} = -62.8$  (s),  $-104.0$  (s),  $-107.3$  (s).

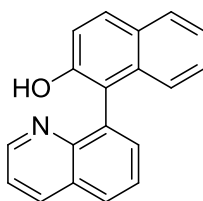
IR (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 2923$  (w), 1628 (w), 1610 (w), 1469 (m), 1352 (m), 1269 (s), 1161 (s), 1019 (m), 1003 (m), 968 (w), 935 (w), 885 (w), 862 (w), 744 (m), 732 (m), 714 (m).

EA ( $\text{C}_{63}\text{H}_{54}\text{BF}_{26}\text{IrNOP}$ ): calc.: C 48.22, H 3.47, N 0.89; found: C 48.54, H 3.55, N 1.26.

$[\alpha]_D^{20} = -24.9$  (c = 0.43,  $\text{CHCl}_3$ ).

### 8.2.3 Pyridine based catalyst with axial chiral backbone

#### 1-(Quinolin-8-yl)naphthalen-2-ol (2.80)



A microwave vial was charged with 1-bromonaphthalen-2-ol (72.9 mg, 327  $\mu\text{mol}$ , 1.00 eq.), quinolin-8-ylboronic acid (100 mg, 392  $\mu\text{mol}$ , 1.20 eq.), allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II) (15.3 mg, 3.0 mol%) and sealed. The vial was purged with argon for 15 min. Afterwards, degassed *i*-PrOH (3 mL) and degassed 4 M NaOH-solution (245  $\mu\text{L}$ ) were added. The solution was stirred for 18 h at 50 °C. The reaction mixture was allowed to cool to room temperature, the resulting dark gel was dissolved in  $\text{CH}_2\text{Cl}_2$  (30 mL) and  $\text{H}_2\text{O}$  (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  30 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated under reduced pressure. Purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 4  $\times$  22 cm, pentane: $\text{Et}_2\text{O}$  (1:1)) afforded the product (35.2 mg, 131  $\mu\text{mol}$ , 40%) as a colorless solid.

$\text{C}_{19}\text{H}_{13}\text{NO}$  (271.32 g/mol):

MP: 183-184 °C.

TLC:  $R_f = 0.23$  ( $\text{SiO}_2$ , pentane: $\text{Et}_2\text{O}$  (1:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.95 (dd,  $^3J_{\text{HH}} = 4.2$ ,  $^4J_{\text{HH}} = 1.8$  Hz, 1H, ar-*H*), 8.38 (dd,  $^3J_{\text{HH}} = 8.3$  Hz,  $^4J_{\text{HH}} = 1.8$  Hz, 1H, ar-*H*), 8.02 (dd,  $^3J_{\text{HH}} = 8.1$  Hz,  $^4J_{\text{HH}} = 1.5$  Hz, 1H, ar-*H*), 7.92 (d,  $^3J_{\text{HH}} = 8.8$  Hz, 1H, ar-*H*), 7.92-7.84 (m, 2H, ar-*H*), 7.76 (dd,  $^3J_{\text{HH}} = 8.1$  Hz,  $^3J_{\text{HH}} = 7.2$  Hz, 1H, ar-*H*), 7.65 (s, 1H, OH), 7.53 (dd,  $^3J_{\text{HH}} = 8.3$  Hz,  $^3J_{\text{HH}} = 4.2$  Hz, 1H, ar-*H*), 7.50-7.42 (m, 1H, ar-*H*), 7.42 (d,  $^3J_{\text{HH}} = 8.9$  Hz, 1H, ar-*H*), 7.38-7.29 (m, 2H, ar-*H*).

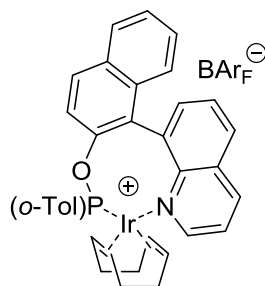
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 151.7 (s, ar- $_{\text{q}}\text{C}$ ), 150.9 (s, ar-*C*), 146.8 (s, ar- $_{\text{q}}\text{C}$ ), 137.9 (s, ar-*C*), 135.1 (s, ar-*C*), 134.7 (s, ar- $_{\text{q}}\text{C}$ ), 134.4 (s, ar- $_{\text{q}}\text{C}$ ), 130.2 (s, ar-*C*), 130.0 (s, ar- $_{\text{q}}\text{C}$ ), 129.2 (s, ar- $_{\text{q}}\text{C}$ ), 128.6 (s, ar-*C*), 128.3 (s, ar-*C*), 126.8 (s, ar-*C*), 126.2 (s, ar-*C*), 125.3 (s, ar-*C*), 123.3 (s, ar-*C*), 121.5 (s, ar-*C*), 120.5 (s, ar- $_{\text{q}}\text{C}$ ), 119.8 (s, ar-*C*).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3334 (m), 3050 (m), 2924 (m), 2641 (m), 1738 (w), 1622 (m), 1595 (m), 1498 (s), 1435 (m), 1341 (m), 1271 (m), 1228 (m), 1132 (w), 1075 (w), 1027 (w), 860 (w), 813 (s), 746 (s), 723 (w), 677 (m), 619 (m).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{19}\text{H}_{14}\text{NO}^+$ : 272.1070  $[\text{M}+\text{H}]^+$ ; found: 272.1072.

**HPLC**: *Daicel*, Chiralpak IC (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 80:20, 0.5 mL/min, 20 °C, 220 nm):  $t_{\text{R}}$  = 12.7 min and 19.5 min.

### Iridium 8-(naphthalen-1-yl)quinoline-di-*o*-tolylphosphinite based catalyst (2.83)



The reaction was set up as described in the general procedure **GP5** except using 1-(quinolin-8-yl)naphthalen-2-ol (22.0 mg, 81.1  $\mu\text{mol}$ , 1.00 eq.), 4-dimethylaminopyridine (11.9 mg, 97.3  $\mu\text{mol}$ , 1.20 eq.) and chloro-di-(2-methylphenyl)-phosphine (30.2 mg, 97.3  $\mu\text{mol}$ , 1.20 eq.) in abs.  $\text{CH}_2\text{Cl}_2$  (1.5 mL). This solution was filtered into  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (27.2 mg, 40.5  $\mu\text{mol}$ , 0.50 eq.) and  $\text{NaBArF}$  (79.0 mg, 89.2  $\mu\text{mol}$ , 1.10 eq.). Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ : 3  $\times$  12 cm, pentane: $\text{CH}_2\text{Cl}_2$  (4:1)  $\rightarrow$  (1:1)) afforded the product (92.0 mg, 55.9  $\mu\text{mol}$ , 69%) as an orange solid.

$\text{C}_{73}\text{H}_{50}\text{BF}_{24}\text{IrNOP}$  (1647.30 g/mol):

**MP:** >97 °C decomposition

**TLC:**  $R_f$  = 0.69 (SiO<sub>2</sub>, pentane:CH<sub>2</sub>Cl<sub>2</sub> (1:2), UV).

**NMRs:** The collected NMR data revealed a complex spectra. In the <sup>31</sup>P NMR two species were detected. The ration of this species changed by switching the solvent to toluene-*d*<sub>8</sub>. The structure could be approved by X-ray crystallography. Crystals suitable for X-ray diffraction were obtained by layering a solution of complex (30 mg) in CD<sub>2</sub>Cl<sub>2</sub> (0.45 mL) with pentane (1.2 mL).

**<sup>31</sup>P{<sup>1</sup>H} NMR** (161 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ/ppm = 96.2 (s), 86.1 (s), ration (100:25).

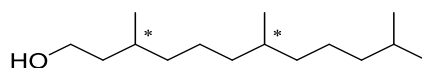
**<sup>31</sup>P{<sup>1</sup>H} NMR** (161 MHz, toluene-*d*<sub>8</sub>): δ/ppm = 96.4 (s), 86.1 (s), ration (100:17).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 1611 (w), 1509 (w), 1466 (w), 1354 (m), 1273 (s), 1116 (s), 973 (w), 949 (w), 886 (m), 826 (m), 778 (w), 753 (m), 712 (m), 670 (m).

**HRMS** (ESI, 4500 V, 180 °C): calc. for C<sub>41</sub>H<sub>38</sub>IrNOP<sup>+</sup>: 784.2317 [M–BAr<sub>F</sub>]<sup>+</sup>; found: 784.2330.

## 8.2.4 Derivatization for the selectivity determination of the hydrogenation of farnesol

### 3,7,11-Trimethyldodecan-1-ol (P15)



(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol (22.2 mg, 0.10 mmol, 1.00 eq.) was dissolved in abs. CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and the iridium complex (1.0 mol%) was added. The vial was charged with a magnetic stirrer, placed in an autoclave and sealed. The autoclave was pressurized to 50 bar with H<sub>2</sub> and the solution was stirred at 800 rpm for 16 h. The hydrogen was released and the reaction mixture concentrated under reduced pressure. The residue was taken up in a mixture of hexane:Et<sub>2</sub>O (1:1, 0.4 mL) and filtered through a plug of SiO<sub>2</sub> (d × h: 0.5 × 2 cm, 5 mL eluent). Evaporation of the solvent afforded the analytically pure product as a colorless oil.

C<sub>15</sub>H<sub>32</sub>O (228.42 g/mol):

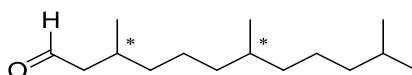
**TLC:**  $R_f$  = 0.30 (SiO<sub>2</sub>, hexane:ethyl acetate (5:1), KMnO<sub>4</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 3.73-3.62 (m, 2H, CH<sub>2</sub>OH), 1.65-1.47 (m, 3H, alkyl-*H*), 1.41-1.02 (m, 14H, alkyl-*H*), 0.89 (d,  $J_{\text{HH}}$  = 6.6 Hz, 3H, CH<sub>3</sub>), 0.86 (d,  $J_{\text{HH}}$  = 6.6 Hz, 6H, CH<sub>3</sub>), 0.84 (d,  $J_{\text{HH}}$  = 6.6 Hz, 3H, CH<sub>3</sub>).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 61.4 (s,  $\text{CH}_2\text{OH}$ ), 40.1 (s, alkyl-C), 39.5 (s, alkyl-C), 37.6 (s, alkyl-C), 37.5 (s, alkyl-C), 37.4 (s, alkyl-C), 32.9 (s, alkyl-C), 29.7 (s, alkyl-C), 28.1 (s, alkyl-C), 24.9 (s, alkyl-C), 24.5 (s, alkyl-C), 22.9 (s, alkyl-C), 22.8 (s, alkyl-C), 19.9 (s, alkyl-C), 19.8 (s, alkyl-C).

Obtained data are in accordance with literature data.<sup>[53b]</sup>

### 3,7,11-Trimethyldodecanal



3,7,11-Trimethyldodecan-1-ol (17.5 mg, 77  $\mu\text{mol}$ , 1.00 eq.) was dissolved in abs.  $\text{CH}_2\text{Cl}_2$  (0.5 mL) and trichloroisocyanuric acid (18.1 mg, 78  $\mu\text{mol}$ , 1.00 eq.) was added. The suspension was stirred for 15 min and cooled down to 0 °C. TEMPO (0.11 mg, 0.9 mol%) was added and the mixture was warmed up to room temperature. The suspension was stirred for 10 min and filtered through a plug of celite (d  $\times$  h: 0.5  $\times$  1 cm). The organic phase was extracted with sat.  $\text{Na}_2\text{CO}_3$  solution (5 mL), 1 N HCl (5 mL) and brine (5 mL). The organic layer was dried over  $\text{MgSO}_4$  and the solvent evaporated in vacuum. The obtained oil was taken up in a mixture of hexane:ethyl acetate (5:1, 0.4 mL) and filtered through a plug of silica (d  $\times$  h: 0.2  $\times$  3 cm, 5 mL eluent) to obtain the product (17.0 mg, 74  $\mu\text{mol}$ , 97%) as a colorless oil.

$\text{C}_{15}\text{H}_{30}\text{O}$  (226.40 g/mol):

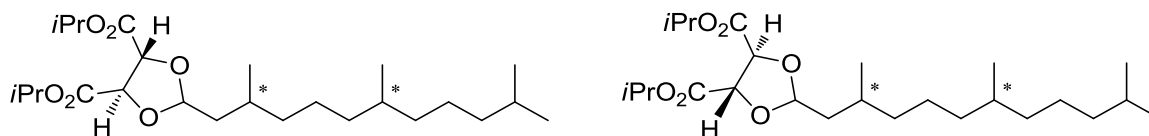
**TLC:**  $R_f$  = 0.75 ( $\text{SiO}_2$ , hexane:ethyl acetate (5:1),  $\text{KMnO}_4$ ).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 9.76 (t,  $J_{\text{HH}}$  = 2.3 Hz, 1H,  $\text{CHO}$ ), 2.39 (ddd,  $J_{\text{HH}}$  = 16.0, 5.7, 1.9 Hz, 1H,  $\text{CH}_2\text{CHO}$ ), 2.22 (ddd,  $J_{\text{HH}}$  = 16.0, 7.8, 2.6 Hz, 1H,  $\text{CH}_2\text{CHO}$ ), 2.09-2.01 (m, 1H, alkyl-H), 1.55-1.48 (m, 1H, alkyl-H), 1.39-1.03 (m, 13H, alkyl-H), 0.97 (d,  $J_{\text{HH}}$  = 6.7 Hz, 3H,  $\text{CH}_3$ ), 0.86 (d,  $J_{\text{HH}}$  = 6.6 Hz, 6H,  $2 \times \text{CH}_3$ ), 0.84 (d,  $J_{\text{HH}}$  = 6.6 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 203.4 (s,  $\text{CHO}$ ), 51.2 (s,  $\text{CH}_2\text{CHO}$ ), 39.5 (s, alkyl-C), 37.4 (s, alkyl-C), 37.4 (s, alkyl-C), 37.3 (s, alkyl-C), 32.9 (s, alkyl-C), 28.4 (s, alkyl-C), 28.1 (s, alkyl-C), 24.9 (s, alkyl-C), 24.5 (s, alkyl-C), 22.9 (s, alkyl-C), 22.8 (s, alkyl-C), 20.2 (s, alkyl-C), 19.9 (s, alkyl-C).

Obtained data are in accordance with literature data.<sup>[53b]</sup>

**(4*R*,5*R*)-Di-iso-propyl 2-(2,6,10-trimethylundecyl)-1,3-dioxolane-4,5-dicarboxylate and (4*S*,5*S*)-di-iso-propyl 2-(2,6,10-trimethylundecyl)-1,3-dioxolane-4,5-dicarboxylate**



3,7,11-Trimethyldodecanal (20 mg, 8.8  $\mu\text{mol}$ , 1.00 eq.) was dissolved in abs.  $\text{CH}_2\text{Cl}_2$  (1 mL). To one half of the above solution was added L-di-iso-propyltartrate (16 mg, 6.6  $\mu\text{mol}$ , 0.75 eq.), to the other half, D-di-iso-propyltartrate (16 mg, 6.6  $\mu\text{mol}$ , 0.75 eq.) was added. Both solutions were cooled down to  $-78^\circ\text{C}$  and trimethylsilyl triflate (4  $\mu\text{L}$ , 22  $\mu\text{mol}$ , 2.80 eq.) was added. The reaction mixture was stirred for 30 min at  $-78^\circ\text{C}$  and for 1.5 h at room temperature.  $\text{Et}_3\text{N}$  (50  $\mu\text{L}$ ) was added to quench the solution. The solvent was evaporated under reduced pressure and taken up in  $\text{Et}_2\text{O}$  (0.4 mL). Filtration over  $\text{SiO}_2$  (0.2  $\times$  1 cm, 3 mL eluent) and evaporation of the ether afforded the L- or the D-acetal as a colorless oil which was used without further purification for GC-analysis.

$\text{C}_{25}\text{H}_{46}\text{O}_6$  (442.64 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 5.30 (t,  $J_{\text{HH}}$  = 5.1 Hz, 1H,  $\text{O}_2\text{CH}$ ), 5.16 (sept,  $J_{\text{HH}}$  = 6.0 Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 5.10 (sept,  $J_{\text{HH}}$  = 6.3 Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 4.64 (d,  $J_{\text{HH}}$  = 4.2 Hz, 1H,  $\text{O}_2\text{CCH}$ ), 4.47 (d,  $J_{\text{HH}}$  = 4.2 Hz, 1H,  $\text{O}_2\text{CCH}$ ), 1.83-1.64 (m, 2H, alkyl-*H*), 1.28 (d,  $J_{\text{HH}}$  = 6.3 Hz, 12H, alkyl-*H*), 1.26-1.10 (m, 12H, alkyl-*H*), 0.95 (d,  $J_{\text{HH}}$  = 6.5 Hz, 3H, alkyl-*H*), 0.85 (d,  $J_{\text{HH}}$  = 6.7 Hz, 6H, alkyl-*H*), 0.83 (d,  $J_{\text{HH}}$  = 6.6 Hz, 6H, alkyl-*H*).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 171.3 (s,  $\text{O}_2\text{C}$ ), 169.7 and 169.0 (s,  $\text{O}_2\text{C}$ ), 107.1 (s,  $\text{OOC}$ ), 77.4 and 77.3 (s,  $\text{O}_2\text{CC}$ ), 72.2 (s,  $\text{O}_2\text{CC}$ ), 70.6 (s,  $\text{CO}_2\text{C}$ ), 69.8 (s,  $\text{CO}_2\text{C}$ ), 40.8 (s, alkyl-*C*), 39.5 (s, alkyl-*C*), 37.8 (s, alkyl-*C*), 37.4 (s, alkyl-*C*), 37.4 (s, alkyl-*C*), 32.9 (s, alkyl-*C*), 29.8 (s, alkyl-*C*), 29.3 (s, alkyl-*C*), 28.1 (s, alkyl-*C*), 24.9 (s, alkyl-*C*), 24.4 (s, alkyl-*C*), 22.9 (s, alkyl-*C*), 22.8 (s, alkyl-*C*), 21.9 (s, alkyl-*C*), 21.8 (s, alkyl-*C*), 19.9 (s, alkyl-*C*), 19.9 (s, alkyl-*C*).

**MS** (FAB NBA):  $m/z$  (%): 443.3 (98), 401.3 (44), 359.2 (45), 245.0 (62), 227.2 (51), 69 (68), 43 (100).

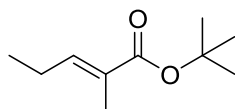
**GC** (CP-Sil 88 (50 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 90 kPa  $\text{H}_2$  (110  $^\circ\text{C}$  – 0 min – 0.5  $^\circ\text{C}/\text{min}$  – 200  $^\circ\text{C}$  – 10 min): L-acetal  $t_{\text{R}}$  = 144.8 min (3*S*,7*R*), 145.4 min [(3*R*,7*S*) + (3*S*,7*S*)], 146.4 min (3*R*,7*R*); D-acetal:  $t_{\text{R}}$  = 144.8 min (3*R*,7*S*), 145.4 min [(3*S*,7*R*) + (3*R*,7*R*)], 146.4 min (3*S*,7*S*).

Obtained data are in accordance with literature data.<sup>[53b]</sup>

### 8.3 Iridium N,P- ligand complexes in the asymmetric hydrogenation of $\alpha,\beta$ -unsaturated carboxylic esters

#### 8.3.1 Synthesis of $\alpha,\beta$ -unsaturated carboxylic esters

##### *tert*-Butyl (*E*)-2-methylpent-2-enoate (3.31)



To a solution of *trans*-2-methyl-2-pentenoic acid (1.80 mL, 1.96 g, 15.4 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) oxalyl chloride (1.33 mL, 1.29 g, 15.5 mmol, 1.00 eq.) and DMF (25  $\mu$ L, 0.02 mmol, 0.01 eq.) were added at 0 °C and the solution was stirred for 10 min at 0 °C. The solution was warmed up to room temperature and stirred overnight. The solution was quenched directly by adding *tert*-butanol (5.00 mL, 3.95 g, 53.3 mmol, 3.50 eq.) followed by Et<sub>3</sub>N (2.13 mL, 15.4 mmol, 1.00 eq.) dropwise at 0 °C. The resulting solution was stirred for 5 h at room temperature. H<sub>2</sub>O (15 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  15 mL). The combined organic layers were dried over MgSO<sub>4</sub>. Column chromatography (SiO<sub>2</sub>, d  $\times$  h: 6  $\times$  15 cm, cyclohexane:ethyl acetate (10:1)) afforded the crude ester as pale brown liquid. Bulb-to-bulb distillation (150 °C, 60 bar) afforded the product (200 mg, 1.18 mmol, 8%) as a colorless liquid.

C<sub>10</sub>H<sub>18</sub>O<sub>2</sub> (170.25 g/mol):

**TLC:** R<sub>f</sub> = 0.74 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (10:1), UV).

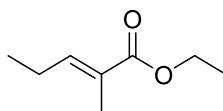
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm: 6.70 (tq, *J* = 7.4, 1.4 Hz, 1H, C=CH). 2.22 (m, 2H, CH<sub>2</sub>), 1.80 (d, *J* = 1.4 Hz, CH<sub>3</sub>), 1.58 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.08 (t, *J* = 7.6 Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 168.2 (s, C=O), 143.1 (s, CH=C), 128.7 (s, CH=C), 80.1 (s, OC(CH<sub>3</sub>)<sub>3</sub>), 28.2 (s, OC(CH<sub>3</sub>)<sub>3</sub>), 22.2 (s, CH<sub>2</sub>), 13.1 (s, CH<sub>3</sub>), 12.3 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 50 °C) *m/z* (%): 114 (51), 69.1 (100), 68.1 (12), 67.1 (19), 55.1 (11), 53.1 (15), 45.0 (15), 43.1 (22), 42.1 (13), 41.1 (99).

**GC** (*Chiral*dex  $\gamma$ -cyclodextrin TFA G-TA (30 m  $\times$  0.25 mm  $\times$  0.12  $\mu$ m), 60 kPa H<sub>2</sub> (45 °C – 25 min – 20 °C/min – 160 °C – 5 min): t<sub>R</sub> = 30.4 min.

Obtained data are in accordance with literature data.<sup>[136]</sup>

**Ethyl (*E*)-2-methylpent-2-enoate (3.26)**

To a solution of *trans*-2-methyl-2-pentenoic acid (1.80 g, 2.00 mL, 15.4 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) oxalyl chloride (1.33 mL, 1.29 g, 15.5 mmol, 1.00 eq.) and DMF (25 μL, 0.02 mmol, 0.01 eq.) were added at 0 °C and the solution was stirred for 10 min at 0 °C. The solution was warmed up to room temperature and stirred overnight. The solution was quenched directly by adding ethanol (5.00 mL, 3.95 g, 85.9 mmol, 5.60 eq.) followed by Et<sub>3</sub>N (2.13 mL, 15.4 mmol, 1.00 eq.) dropwise at 0 °C. The resulting solution was stirred for 5 h at room temperature. H<sub>2</sub>O (15 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined organic layers were dried over MgSO<sub>4</sub>. Column chromatography (SiO<sub>2</sub>, d × h: 5 × 16 cm, pentane:Et<sub>2</sub>O (40:1)) afforded the product (1.21 g, 8.52 mmol, 55%) as a colorless liquid.

C<sub>8</sub>H<sub>14</sub>O<sub>2</sub> (142.20 g/mol):

**TLC:** R<sub>f</sub> = 0.31 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (30:1), UV).

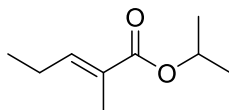
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 6.72 (t, *J* = 6.8 Hz, 1H, C=CH), 4.19 (q, *J* = 6.7 Hz, 2H, OCH<sub>2</sub>), 2.20 (m, 2H, CH<sub>2</sub>), 1.84 (s, 3H, CH<sub>3</sub>), 1.32 (t, *J* = 6.7 Hz, 3H, CH<sub>3</sub>), 1.08 (t, *J* = 7.5 Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 167.4 (s, CO<sub>2</sub>), 144.3 (s, CH=C), 127.8 (s, CH=C), 59.6 (s, OCH<sub>2</sub>), 21.5 (s, CH<sub>2</sub>), 13.1 (s, CH<sub>3</sub>), 12.7 (s, CH<sub>3</sub>), 12.1 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 142.1 (25), 114.1 (22), 113.1 (19), 97.1 (42), 69.1 (100), 67.1 (17), 43.1 (13), 41.1 (72).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 36.07 min.

Obtained data are in accordance with literature data.<sup>[137]</sup>

**(E)-Isopropyl 2-methylpent-2-enoate (3.27)**

To a solution of *trans*-2-methyl-2-pentenoic acid (1.80 g, 2.00 mL, 15.4 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) oxalyl chloride (1.33 mL, 1.29 g, 15.5 mmol, 1.00 eq.) and DMF (25  $\mu$ L, 0.02 mmol, 0.01 eq.) were added at 0 °C and the solution was stirred for 10 min at 0 °C. The solution was warmed up to room temperature and stirred overnight. The solution was quenched directly by adding isopropanol (5.00 mL, 65.0 mmol, 4.02 eq.) followed by Et<sub>3</sub>N (2.13 mL, 15.4 mmol, 1.00 eq.) dropwise at 0 °C. The resulting solution was stirred for 5 h at room temperature. H<sub>2</sub>O (15 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  15 mL). The combined organic layers were dried over MgSO<sub>4</sub>. Column chromatography (SiO<sub>2</sub>, d  $\times$  h: 5  $\times$  16 cm, pentane:Et<sub>2</sub>O (40:1)) afforded the product (1.50 g, 9.61 mmol, 62%) as a colorless liquid.

C<sub>9</sub>H<sub>16</sub>O<sub>2</sub> (156.22 g/mol):

**TLC:** R<sub>f</sub> = 0.41 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (40:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 6.70 (t, <sup>3</sup>J<sub>HH</sub> = 7.3 Hz, 1H, C=CH), 5.03 (sept, <sup>3</sup>J<sub>HH</sub> = 6.2 Hz, 1H, OCH(CH<sub>3</sub>)<sub>2</sub>), 2.19-2.12 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>), 1.79 (s, 3H, C=CHCH<sub>3</sub>), 1.24 (d, <sup>3</sup>J<sub>HH</sub> = 6.3 Hz, 6H, OCH(CH<sub>3</sub>)<sub>2</sub>), 1.03 (t, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 168.1 (s, CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 143.5 (s, C=CH), 127.8 (s, C=CH), 67.7 (s, CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 22.1 (s, CH<sub>3</sub>CH<sub>2</sub>), 22.1 (s, CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 13.2 (s, CH<sub>3</sub>), 12.3 (s, CH<sub>3</sub>).

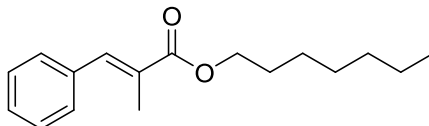
**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 2975 (w), 2954 (w), 2876 (w), 1704 (s), 1646 (w), 1455 (w), 1386 (w), 1372 (m), 1268 (m), 1243 (s), 1180 (w), 1165 (w), 1146 (m), 1111 (s), 1099 (s), 1087 (s), 1035 (w), 929 (w), 898 (w), 844 (w), 741 (w).

**MS** (EI, 70 eV, Inlet 150 °C) *m/z* (%): 156.1 (5), 127 (42), 115.0 (23), 114.0 (52), 97.0 (95), 69 (100), 59.0 (13), 43 (44), 41 (55), 39 (11).

**EA** (C<sub>9</sub>H<sub>16</sub>O<sub>2</sub>): calc.: C 69.19, H 10.32; found: C 68.94, H 10.18.

**GC** (Chiraldex  $\gamma$ -cyclodextrin TFA G-TA (30 m  $\times$  0.25 mm  $\times$  0.12  $\mu$ m), 60 kPa H<sub>2</sub> (45 °C – 25 min – 20 °C/min – 160 °C – 5 min): t<sub>R</sub> = 28.4 min.



**(E)-Heptyl 2-methyl-3-phenylacrylate (3.5)**

To a solution of  $\alpha$ -methylcinnamic acid (1.50 g, 9.25 mmol, 1.00 eq.) in  $\text{CH}_2\text{Cl}_2$  (10 mL) oxalyl chloride (1.56 mL, 2.34 g, 18.5 mmol, 2.00 eq.) and DMF (70  $\mu\text{L}$ , 0.09 mmol, 0.01 eq.) were added at 0 °C and the solution was stirred for 10 min at 0 °C. The solution was warmed up to room temperature and stirred overnight. All volatiles were evaporated in HV. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) and heptanol (3.00 mL, 21.2 mmol, 2.20 eq.) followed by  $\text{Et}_3\text{N}$  (1.50 mL, 10.8 mmol, 1.20 eq.) were added dropwise at 0 °C. The resulting solution was stirred for 16 h at room temperature.  $\text{H}_2\text{O}$  (15 mL) was added and followed by extraction with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 15$  mL). The combined organic layers were dried over  $\text{MgSO}_4$ . Column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 12$  cm, cyclohexane:ethyl acetate (40:1)) afforded the crude ester. The ester was further purified via bulb-to-bulb distillation to afford the product (1.70 g, 6.53 mmol, 71%) as a colorless liquid.

$\text{C}_{17}\text{H}_{24}\text{O}_2$  (260.38 g/mol):

**BP:** 155 °C (0.6 mbar).

**TLC:**  $R_f$  = 0.56 ( $\text{SiO}_2$ , cyclohexane:ethyl acetate (40:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.69 (q,  $^4J_{\text{HH}}$  = 1.4 Hz,  $\text{C}=\text{CH}$ , 1H), 7.42-7.37, (m, ar- $H$ , 4H), 7.35-7.30 (m, ar- $H$ , 1H), 4.21 (t,  $^3J_{\text{HH}}$  = 6.7 Hz,  $\text{OCH}_2$ , 2H), 2.13 (d,  $^4J_{\text{HH}}$  = 1.5 Hz, 3H,  $\text{CH}=\text{CCH}_3$ ), 1.76-1.69 (m, 2H,  $\text{OCH}_2\text{CH}_2$ ), 1.44-1.30 (m, 8H, alkyl- $H$ ), 0.90 (t,  $^3J_{\text{HH}}$  = 6.71 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 168.9 (s,  $\text{COO}$ ), 138.8 (s,  $\text{HC}=\text{C}$ ), 136.2 (s, ar- $q\text{C}$ ), 129.8 (s, ar- $\text{C}$ ), 128.9 (s,  $\text{HC}=\text{C}$ ), 128.5 (s, ar- $\text{C}$ ), 128.4 (s, ar- $\text{C}$ ), 65.3 (s,  $\text{OCH}_2$ ), 31.9 (s,  $\text{CH}_2$ ), 29.2 (s,  $\text{CH}_2$ ), 28.9 (s,  $\text{CH}_2$ ), 26.2 (s,  $\text{CH}_2$ ), 22.8 (s,  $\text{CH}_2$ ), 14.3 (s,  $\text{CH}_3$ ), 14.3 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3027 (w), 2955 (m), 2926 (m), 1705 (s), 1636 (m), 1491 (m), 1448 (m), 1356 (w), 1294 (w), 1245 (s), 1200 (m), 1111 (s), 1074 (w), 1030 (w), 1003 (m), 928 (m), 764 (m), 738 (w).

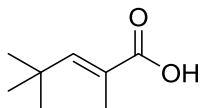
**MS** (EI, 70 eV, 50 °C)  $m/z$  (%): 260.2 (21), 163.1 (21), 162.1 (100), 161.1 (23), 145.1 (42), 117.1 (44), 116.1 (37), 115.1 (26), 91.1 (11), 57.1 (13).

**EA** ( $\text{C}_{17}\text{H}_{24}\text{NO}_2$ ): calc.: C 78.42, H 9.29; found: C 78.44, H 9.45.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 26.32 min.

**HPLC:** *Daicel* Chiralcel OJ (0.46 cm × 25 cm, heptane, 0.5 mL/min; T = 25 °C, 220 nm,  $t_R$  = 17.9 min.

**(E)-2,4,4-Trimethylpent-2-enoic acid**



A mixture of NaH (60% in mineral oil, 2.40 g, 60 mmol, 3.00 eq.) and diethyl phosphite (2.56 mL, 20.0 mmol, 1.00 eq.) in THF (50 mL) was treated with a solution of  $\alpha$ -bromopropionic acid (1.79 mL, 20.0 mmol, 1.00 eq.) acid in THF (20 mL). After gas evolution had ceased, pivalaldehyde (2.17 mL, 20.0 mmol, 1.00 eq.) was added and the reaction mixture was stirred for 2 d at room temperature. Ethanol (5 mL) was added and the reaction mixture was poured into H<sub>2</sub>O (150 mL). The solution was washed with MTBE (50 mL) and the aqueous phased acidified to a pH of 2-3 with 10% aqueous HCl. The mixture was extracted with MTBE (3 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure and the crude product was purified by bulb-to-bulb distillation to afford the product (1.24 g, 8.72 mmol, 44%) as a colorless solid.

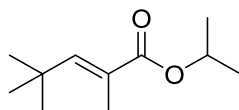
C<sub>8</sub>H<sub>14</sub>O<sub>2</sub> (142.20 g/mol):

**BP:** 182 °C (44 mbar).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 12.54 (s br, 1H, CO<sub>2</sub>H), 6.82 (m, 1H, C=CH), 1.84 (d, 1.3 Hz, CH<sub>3</sub>), 1.18 (s, 1H, C(CH<sub>3</sub>)<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 176.1 (s, CO<sub>2</sub>H), 152.4 (s, CH=C), 126.2 (s, CH=C), 33.1 (s, C(CH<sub>3</sub>)<sub>3</sub>), 30.3 (s, C(CH<sub>3</sub>)<sub>3</sub>), 13.6 (s, CH=CCH<sub>3</sub>).

Obtained data are in accordance with literature data.<sup>[138]</sup>

**Isopropyl (*E*)-2,4,4-trimethylpent-2-enoate (3.32)**

To a solution of (*E*)-2,4,4-trimethylpent-2-enoic acid (700 mg, 4.92 mmol, 1.00 eq.) in  $\text{CH}_2\text{Cl}_2$  (5 mL) oxalyl chloride (1.28 g, 840  $\mu\text{L}$ , 9.84 mmol, 2.00 eq.) and DMF (5  $\mu\text{L}$ ) were added dropwise at 0 °C. The yellow reaction mixture was stirred for 16 h at room temperature followed by the addition of iso-propanol (1.56 g, 2.00 mL, 26.0 mmol, 11.1 eq.) and  $\text{Et}_3\text{N}$  (365 mg, 500  $\mu\text{L}$ , 3.61 mmol, 1.60 eq.) at 0 °C. The solution was stirred for 4 h at room temperature and the solvent was evaporated under reduced pressure. Purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 3  $\times$  25 cm, cyclohexane:ethyl acetate (25:1)) afforded the product as a colorless liquid (504 mg, 2.74 mmol, 57%).

$\text{C}_{11}\text{H}_{20}\text{O}_2$  (184.28 g/mol):

**TLC:**  $R_f$  = 0.67 ( $\text{SiO}_2$ , cyclohexane:ethyl acetate (10:1), UV).

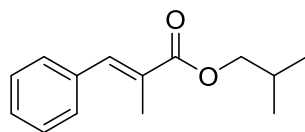
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 6.76 (q,  $J$  = 1.36 Hz, 1H,  $\text{CH}=\text{C}$ ), 5.01 (sept,  $J$  = 6.2 Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 1.92 (d,  $J$  = 1.4 Hz, 3H,  $\text{CH}_3$ ), 1.24 (d,  $J$  = 6.3 Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 1.16 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 169.0 (s,  $\text{CO}_2(\text{C}(\text{CH}_3)_3)$ ), 150.9 (s,  $\text{CH}=\text{C}$ ), 127.2 (s,  $\text{CH}=\text{C}$ ), 67.9 (s,  $\text{OC}(\text{CH}_3)_3$ ), 33.1 (s,  $\text{C}(\text{CH}_3)_3$ ), 30.3 (s,  $\text{C}(\text{CH}_3)_3$ ), 22.1 (s,  $\text{CH}(\text{CH}_3)_2$ ), 13.4 (s,  $\text{CH}=\text{CCH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2961 (w), 2873 (w), 1733 (m), 1707 (m), 1640 (w), 1468 (m), 1367 (m), 1251 (m), 1200 (m), 1181 (m), 1146 (m), 1102 (s), 1015 (w), 929 (w), 848 (w), 826 (w), 748 (w), 671 (w).

**MS** (EI, 70 eV, 50 °C)  $m/z$  (%): 184.1 (1), 142.1 (49), 127.1 (100), 125.1 (34), 109.1 (41), 97.1 (16), 84.1 (18), 81.1 (25), 69.1 (10), 59.1 (31), 55.1 (23), 43.1 (28), 41.1 (31).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 9.48 min.

**Isobutyl (*E*)-2-methyl-3-phenylacrylate (3.8)**

To a solution of (*E*)-2-methyl-3-phenylacrylic acid (1.50 g 9.26 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) oxalyl chloride (1.54 mL, 1.50 g, 18.0 mmol, 1.90 eq.) and DMF (10 μL, 0.04 mmol, 0.01 eq.) were added at 0 °C and the solution was stirred for 10 min at 0 °C. The solution was warmed up to room temperature and stirred overnight. All volatiles were evaporated in HV to afford the crude acid chloride which was used without further purification. The acid chloride was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and iso-butanol (1.60 g, 2.00 mL, 21.6 mmol, 2.30 eq.) and Et<sub>3</sub>N (1.09 g, 1.50 mL, 10.8 mmol, 1.20 eq.) were added dropwise at 0 °C. The solution was stirred for 6 h at room temperature and all volatiles were evaporated in HV. Purification by column chromatography (SiO<sub>2</sub>, d × h: 6 × 20 cm, cyclohexane:ethyl acetate (50:1→30:1)) afforded the product as a colorless liquid (1.68 g, 7.71mmol, 83%).

C<sub>14</sub>H<sub>18</sub>O<sub>2</sub> (218.30 g/mol):

**TLC:** R<sub>f</sub> = 0.28 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (50:1), UV).

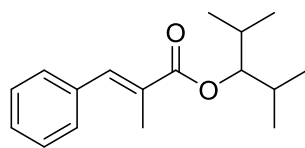
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.71 (d, *J* = 1.3 Hz, 1H, CH=C), 7.46-7.36 (m, 4H, ar-*H*), 7.35-7.27 (m, 1H, ar-*H*), 4.01 (d, *J* = 6.6 Hz, 2H, OCH<sub>2</sub>), 2.14 (d, *J* = 1.4 Hz, 3H, CH<sub>3</sub>), 2.10-2.00 (m, 1H, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.01 (d, *J* = 6.7 Hz, 6H, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 168.9 (s, CO<sub>2</sub>), 138.8 (s, CH=C), 136.1 (s, ar-*qC*), 129.8 (s, ar-*C*), 128.8 (s, CH=C), 128.5 (s, ar-*C*), 128.4 (s, ar-*C*), 71.5 (s, OCH<sub>2</sub>), 28.0 (s, OCH<sub>2</sub>CH), 19.4 (s, CH<sub>3</sub>), 14.2 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2961 (m), 2975 (w), 1707 (s), 1635 (w), 1470 (w), 1448 (w), 1376 (w), 1248 (s), 1201 (m), 1114 (s), 929 (w), 765 (w), 704 (w), 634 (w).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 218.1 (26), 163.1 (13), 162.1 (96), 161.1 (40), 146.1 (11), 145.1 (89), 118.1 (13), 117.1 (100), 116.1 (84), 115.1 (76), 91.1 (25), 57.1 (13), 41.1 (17).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 31.65 min.

**2,4-Dimethylpentan-3-yl (*E*)-2-methyl-3-phenylacrylate**

To a solution of (*E*)-2-methyl-3-phenylacrylic acid (1.50 g 9.26 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) oxalyl chloride (1.54 mL, 1.50 g, 18.0 mmol, 1.90 eq.) and DMF (10 μL, 0.04 mmol, 0.01 eq.) were added at 0 °C and the solution was stirred for 10 min at 0 °C. The solution was warmed up to room temperature and stirred overnight. All volatiles were evaporated in HV to afford the crude acid chloride which was used without further purification. The acid chloride was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and 2,4-dimethylpentan-3-ol (4.14 g, 5.00 mL, 35.7 mmol, 11.0 eq.) and Et<sub>3</sub>N (1.41 g, 1.92 mL, 13.9 mmol, 1.60 eq.) were added dropwise at 0 °C. The solution was stirred for 6 h at room temperature and all volatiles were evaporated in HV. Purification by column chromatography (SiO<sub>2</sub>, d × h: 3 × 30 cm, cyclohexane:ethyl acetate (80:1)) afforded the product as a colorless liquid (2.09 g, 8.06 mmol, 87%).

C<sub>17</sub>H<sub>24</sub>O<sub>2</sub> (260.38 g/mol):

**TLC:** R<sub>f</sub> = 0.47 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (50:1), UV).

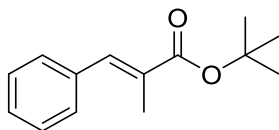
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.71 (d, <sup>4</sup>J<sub>HH</sub> = 1.1 Hz, 1H, C=CH), 7.43-7.37 (m, 4H, ar-H), 7.35-7.29 (m, 1H, ar-H), 4.75 (t, <sup>3</sup>J<sub>HH</sub> = 6.1 Hz, 1H, OCH(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 2.14 (d, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 3H C=CCH<sub>3</sub>), 2.03-1.95 (m, 2H, OCH(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 0.93 (d, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz, 12H OCH(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 168.9 (s, C=O), 138.6 (s, HC=C), 136.2 (s, ar-qC), 129.9 (s, ar-C), 129.0 (s, HC=C), 128.5 (s, ar-C), 128.4 (s, ar-C), 83.3 (s, OCH(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 29.8 (s, OCH(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 19.8 (s, OCH(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 17.6 (s, OCH(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 14.4 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2965 (m), 2935 (w), 2876 (w), 1704 (s), 1636 (w), 1465 (w), 1388 (w), 1369 (w), 1324 (w), 1248 (s), 1201 (m), 1112 (s), 1002 (w), 952 (m), 906 (w), 763 (w), 702 (m), 625 (m).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 260.1 (2), 162.1 (29), 146.1 (12), 117.1 (34), 116.1 (15), 115.1 (29), 98.1 (19), 91.1 (10), 83.1 (16), 43.1 (10).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 22.90 min.

***tert*-Butyl (*E*)-2-methyl-3-phenylacrylate**

To a solution of (*E*)-2-methyl-3-phenylacrylic acid (1.50 g 9.26 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) oxalyl chloride (1.54 mL, 1.50 g, 18.0 mmol, 1.90 eq.) and DMF (10 μL, 0.04 mmol, 0.01 eq.) were added at 0 °C and the solution was stirred for 10 min at 0 °C. The solution was warmed up to room temperature and stirred overnight. All volatiles were evaporated in HV to afford the crude acid chloride which was used without further purification. The acid chloride was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and 2,4-dimethylpentan-3-ol (2.64 g, 2.97 mL, 35.7 mmol, 11.0 eq.) and Et<sub>3</sub>N (1.41 g, 1.92 mL, 13.9 mmol, 1.60 eq.) were added dropwise at 0 °C. The solution was stirred for 6 h at room temperature and all volatiles were evaporated in HV. Purification by column chromatography (SiO<sub>2</sub>, d × h: 3 × 30 cm, cyclohexane:ethyl acetate (80:1)) afforded the product as a colorless liquid (305 g, 1.40 mmol, 15%).

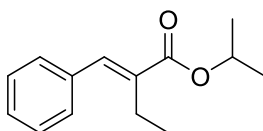
C<sub>14</sub>H<sub>18</sub>O<sub>2</sub> (218.30 g/mol):

**TLC:** R<sub>f</sub> = 0.72 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (50:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.60 (s, 1H, CH=C), 7.38 (d, *J* = 4.4 Hz, 4H, ar-*H*), 7.34-7.27 (m, 1H, ar-*H*), 2.07 (d, *J* = 1.4 Hz, 3H, CH<sub>3</sub>), 1.55 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 168.1 (s, CO<sub>2</sub>), 138.0 (s, CH=C), 136.4 (ar-*q*C), 130.4 (s, C=CH), 129.7 (s, ar-C), 128.5 (s, ar-C), 128.2 (s, ar-C), 80.7 (s, OC(CH<sub>3</sub>)<sub>3</sub>), 28.3 (s, OC(CH<sub>3</sub>)<sub>3</sub>), 14.3 (s, CH<sub>3</sub>).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 18.50 min.

**(*E*)-Isopropyl 2-benzylidenebutanoate (3.14)**

To a solution of (*E*)-2-benzylidenebutanoic acid (750 mg 4.26 mmol, 1.00 eq.), prepared according to literature know procedure<sup>[72]</sup>, in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) oxalyl chloride (0.73 mL, 0.71 g, 8.52 mmol, 2.00 eq.) and DMF (30 μL, 0.04 mmol, 0.01 eq.) were added at 0 °C and the

solution was stirred for 10 min at 0 °C. The solution was warmed up to room temperature and stirred overnight. All volatiles were evaporated in HV. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and isopropanol (1.31 mL, 17.0 mmol, 4.00 eq.) and Et<sub>3</sub>N (0.59 mL, 4.26 mmol, 1.00 eq.) were added dropwise at 0 °C. The reaction mixture was stirred for 5 h at room temperature. H<sub>2</sub>O (15 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined organic layers were dried over MgSO<sub>4</sub>. Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 16 cm, pentane:Et<sub>2</sub>O (50:1)) followed by bulb-to-bulb distillation afforded the product (190 mg, 0.87 mmol, 20%) as a colorless liquid.

C<sub>14</sub>H<sub>18</sub>O<sub>2</sub> (218.30 g/mol):

**BP:** 100 °C (0.6 mbar).

**TLC:** R<sub>f</sub> = 0.42 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (50:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.63 (s, 1H, C=CH), 7.40–7.36 (m, 4H, ar-*H*), 7.33–7.29 (m, 1H, ar-*H*), 5.16 (sept, <sup>3</sup>J<sub>HH</sub> = 6.3 Hz, 1H, OCH(CH<sub>3</sub>)<sub>2</sub>), 2.54 (q, <sup>3</sup>J<sub>HH</sub> = 7.4 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.33 (d, <sup>3</sup>J<sub>HH</sub> = 6.3 Hz, 6H, OCH(CH<sub>3</sub>)<sub>2</sub>), 1.18 (t, <sup>3</sup>J<sub>HH</sub> = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

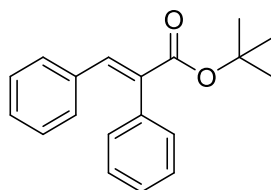
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 168.0 (s, COOCH(CH<sub>3</sub>)<sub>2</sub>), 138.2 (s, CH=CCO<sub>2</sub>), 136.1 (s, ar-*C*), 135.6 (s, ar-*C*), 129.3 (s, ar-*C*), 128.6 (s, ar-*C*), 128.3 (s, CH=CCO<sub>2</sub>), 68.2 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 22.1 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 21.0 (s, CH<sub>2</sub>CH<sub>3</sub>), 14.1 (s, CH<sub>2</sub>CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3059 (w), 3024 (w), 2978 (m), 2935 (m), 1703 (s), 1632 (m), 1465 (w), 1446 (w), 1373 (m), 1284 (w), 1236 (s), 1202 (m), 1180 (w), 1132 (m), 1106 (s), 1038 (w), 966 (w), 928 (w), 766 (w), 700 (m).

**MS** (EI, 70 eV, RT) *m/z* (%): 218.1 (55), 176.1 (49), 175.1 (25), 161.1 (11), 159.2 (56), 158.2 (41.1), 132.1 (13), 131.1 (100), 130.1 (79), 117.0 (17), 116.0 (16), 115.0 (36), 91 (41), 43 (14).

**EA** (C<sub>14</sub>H<sub>18</sub>O<sub>2</sub>) calc.: C 77.03, H 8.31; found: C 76.64, H 8.42.

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 18.69 min.

**(E)-tert-Butyl 2,3-diphenylacrylate (3.18)**

To a solution of (*E*)-2,3-diphenylacrylic acid (5.00 mg, 22.3 mmol, 1.00 eq.) in  $\text{CH}_2\text{Cl}_2$  (50 mL) oxalyl chloride (5.62 mg, 3.80 mL, 44.6 mmol, 2.00 eq.) and DMF (50  $\mu\text{L}$ ) were added dropwise at 0 °C. The yellow reaction mixture was stirred for 16 h at room temperature and all volatiles were evaporated in HV to afford the acid chloride as a brownish solid which was used without further purification. The acid chloride was dissolved in  $\text{CH}_2\text{Cl}_2$  (30 mL) and *tert*-butanol (5.53 g, 7.00 mL, 74.6 mmol, 11.1 eq.) and  $\text{Et}_3\text{N}$  (3.65 g, 5.00 mL, 36.1 mmol, 1.60 eq.) were added dropwise at 0 °C. The solution was stirred for 4 h at room temperature and all volatiles were evaporated in HV. Purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 3  $\times$  20 cm, cyclohexane:ethyl acetate (25:1)) afforded the product as a colorless solid (1.56 g, 5.57 mmol, 25%).

$\text{C}_{19}\text{H}_{20}\text{O}_2$  (280.37 g/mol):

**MP:** 70-71 °C.

**TLC:**  $R_f$  = 0.43 ( $\text{SiO}_2$ , cyclohexane:ethyl acetate (20:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.73 (s, 1H, C=CH), 7.37-7.31 (m, 3H, ar-*H*), 7.22-7.12 (m, 5H, ar-*H*), 7.06-7.03 (m, 3H, ar-*H*), 1.51 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 167.2 (s, COO), 139.2 (s, CH=C), 136.5, 135.2, 134.6, 130.7, 130.0, 128.9, 128.6, 128.3, 127.7, 81.3 (s, OC(CH<sub>3</sub>)<sub>3</sub>), 28.3 (s, OC(CH<sub>3</sub>)<sub>3</sub>).

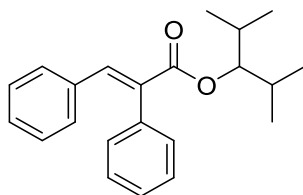
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3057 (w), 2982 (w), 2928 (w), 1699 (s), 1621 (m), 1574 (w), 1493 (w), 1446 (m), 1366 (m), 1246 (s), 1210 (w), 1149 (s), 1078 (w), 1032 (w), 995 (m), 947 (w), 882 (w), 846 (w), 761 (m), 713 (m), 691 (s).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 280.2 (26), 225.1 (16), 224.1 (91), 207.1 (12), 180.1 (18), 179.1 (100), 178.1 (56), 152.1 (10), 118.1 (23), 57.1 (27).

**EA** ( $\text{C}_{19}\text{H}_{20}\text{O}_2$ ): calc. C 81.40, H 7.19; found: C 81.33, H 7.16.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 25.90 min.



**(E)-2,4-Dimethylpentan-3-yl 2,3-diphenylacrylate (3.19)**

To a solution of (*E*)-2,3-diphenylacrylic acid (750 mg, 3.25 mmol, 1.00 eq.) in  $\text{CH}_2\text{Cl}_2$  (20 mL) oxalyl chloride (390 mg, 260  $\mu\text{L}$ , 6.50 mmol, 2.00 eq.) and DMF (5  $\mu\text{L}$ ) were added dropwise at 0 °C. The yellow reaction mixture was stirred for 6 h at room temperature and all volatiles were evaporated in HV to afford the acid chloride as a brownish solid which was used without further purification. The acid chloride was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL) and 2,4-dimethylpentan-3-ol (2.90 g, 3.50 mL, 25.0 mmol, 7.70 eq.) and  $\text{Et}_3\text{N}$  (548 mg, 750  $\mu\text{L}$ , 5.42 mmol, 1.60 eq.) were added dropwise at 0 °C. The solution was stirred for 6 h at room temperature and all volatiles were evaporated in HV. Purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 3  $\times$  30 cm, cyclohexane:ethyl acetate (30:1)) afforded the product as a colorless solid (805 mg, 2.50 mmol, 77%).

$\text{C}_{22}\text{H}_{26}\text{O}_2$  (322.45 g/mol):

**MP:** 70-72 °C.

**TLC:**  $R_f$  = 0.47 ( $\text{SiO}_2$ , cyclohexane:ethyl acetate (30:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.85 (s, 1H,  $\text{CH}=\text{C}$ ), 7.39-7.31 (m, 3H, ar-*H*), 7.23-7.06 (m, 7H, ar-*H*), 4.71 (t,  $J_{\text{HH}}$  = 6.1 Hz, 1H,  $\text{OCH}(\text{CH}(\text{CH}_3)_2)_2$ ), 1.93-1.81 (m, 2H,  $\text{OCH}(\text{CH}(\text{CH}_3)_2)_2$ ), 0.89 (d,  $J_{\text{HH}}$  = 6.8 Hz, 6H,  $\text{OCH}(\text{CH}(\text{CH}_3)_2)_2$ ), 0.80 (d,  $J_{\text{HH}}$  = 6.7 Hz, 6H,  $\text{OCH}(\text{CH}(\text{CH}_3)_2)_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 168.1 (s,  $\text{PhCH}=\text{CPh}-\text{CO}_2$ ), 140.0 (s,  $\text{PhCH}=\text{C}-\text{CO}_2$ ), 136.6 (s, ar- $q\text{C}$ ), 135.0 (s,  $\text{PhCH}=\text{CPh}-\text{COO}$ ), 133.4 (s, ar- $q\text{C}$ ), 130.8 (s, arC), 129.8 (s, ar-C), 129.1 (s, ar-C), 128.7 (s, ar-C), 128.4 (s, arC), 127.7 (s, ar-C), 83.7 (s,  $\text{OCH}(\text{CH}(\text{CH}_3)_2)_2$ ), 29.7 (s,  $\text{OCH}(\text{CH}(\text{CH}_3)_2)_2$ ), 19.8 (s,  $\text{OCH}(\text{CH}(\text{CH}_3)_2)_2$ ), 17.4 (s,  $\text{OCH}(\text{CH}(\text{CH}_3)_2)_2$ ).

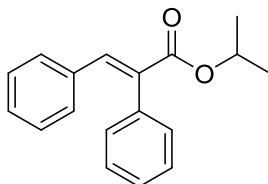
**MS** (EI, 70 eV, 50 °C)  $m/z$  (%): 322.2 (25), 225.1 (14), 224.1 (93), 207.1 (55), 180.1 (14), 179.1 (100), 178.1 (46).

**EA** ( $\text{C}_{22}\text{H}_{26}\text{O}_2$ ): calc. C 81.95, H 8.13; found: C 81.66, H 8.09.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 31.65 min.

**HPLC:** *Daicel* Chiralpak AD-H (0.46 cm × 25 cm, heptane/iso-propanol 99:01, 0.5 mL/min; T = 20 °C, 220 nm,  $t_R$  = 16.1 min.

**Isopropyl (*E*)-2,3-diphenylacrylate (3.17)**



To a solution of (*E*)-2,3-diphenylacrylic acid (500 mg, 2.23 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) oxalyl chloride (260 mg, 173 μL, 4.46 mmol, 2.00 eq.) and DMF (5 μL) were added dropwise at 0 °C. The yellow reaction mixture was stirred for 16 h at room temperature and all volatiles were evaporated in HV to afford the acid chloride as a brownish solid which was used without further purification. The acid chloride was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and iso-propanol (1.56 g, 2.00 mL, 26.0 mmol, 11.1 eq.) and Et<sub>3</sub>N (365 mg, 500 μL, 3.61 mmol, 1.60 eq.) were added dropwise at 0 °C. The solution was stirred for 4 h at room temperature and all volatiles were evaporated in HV. Purification by column chromatography (SiO<sub>2</sub>, d × h: 3 × 20 cm, cyclohexane:ethyl acetate (20:1)) afforded the product as a colorless solid (404 mg, 1.52 mmol, 68%).

C<sub>18</sub>H<sub>18</sub>O<sub>2</sub> (266.34 g/mol):

**MP:** 65-66 °C.

**TLC:**  $R_f$  = 0.33 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (20:1), UV).

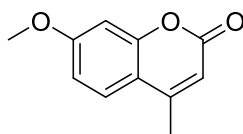
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.80 (s, 1H, C=CH), 7.38-7.33 (m, 3H, ar-*H*), 7.23-7.13 (m, 5H, ar-*H*), 7.07-7.03 (m, 2H, ar-*H*), 5.14 (sept, <sup>3</sup> $J_{HH}$  = 6.3 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.28 (d,  $J_{HH}$  = 6.3 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 167.5, 139.9, 136.2, 135.0, 133.5, 130.7, 130.0, 129.0, 128.7, 128.3, 127.9, 68.8, 22.1.

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 267.1 (16), 266.1 (80), 224.0 (16), 208.1 (17), 207.0 (12), 180.1 (19), 179.1 (100), 178.1 (71), 177.1 (10), 176.1 (12), 152.1 (14), 118.1 (23), 107.1 (32), 43.1 (14).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 25.64 min.

Obtained data are in accordance with literature data.<sup>[139]</sup>

**7-Methoxy-4-methyl-2H-chromen-2-one (3.37)**

A solution of 7-hydroxy-4-methyl-coumarin (1.00 g, 5.60 mmol, 1.00 eq.) in DMF (12 mL) was cooled to 0 °C and NaH (60% in mineral oil, 268 mg, 6.72 mmol, 1.20 eq.) was added in small portions. The reaction mixture was stirred for 30 min at room temperature followed by cooling to 0 °C. Methyl iodide (0.42 mL, 953 mg, 6.72 mmol, 1.20 eq.) was added dropwise and the reaction mixture was stirred for 3 h at room temperature. All volatiles were evaporated in HV to afford a yellow residue. Purification by column chromatography (SiO<sub>2</sub>, d × h: 6 × 26 cm, cyclohexane:ethyl acetate (10:1→2:1)) afforded the product (1.02 g, 5.32 mmol, 95%) as a colorless solid.

C<sub>11</sub>H<sub>10</sub>O<sub>3</sub> (190.20 g/mol):

**MP:** 156–157 °C.

**TLC:** R<sub>f</sub> = 0.15 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (7:1), UV).

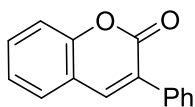
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.48 (d, *J* = 8.8 Hz, 1H, ar-*H*), 6.85 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1H, ar-*H*), 6.79 (d, *J* = 2.5 Hz, 1H, ar-*H*), 6.11 (s, 1H, C=CH), 3.86 (s, 3H, OCH<sub>3</sub>), 2.38 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 162.8, 161.5, 155.5, 152.8, 125.7, 113.7, 112.4, 112.1, 101.0, 55.9 (s, OCH<sub>3</sub>), 18.8 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 191.0 (10), 190.1 (81), 162.1 (81), 148.1 (10), 147.1 (100), 91.1 (26), 77.1 (10), 65.1 (17).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 28.51 min.

Obtained data are in accordance with literature data.<sup>[140]</sup>

**3-Phenyl-2H-chromen-2-one (3.36)**

A mixture of 2-hydroxybenzaldehyde (1.97 mL, 2.69 g, 22.0 mmol, 1.00 eq.), phenyl acetic acid (3.00 g, 22.0 mmol, 1.00 eq.), acetic anhydride (6.65 mL, 7.18 g, 70.3 mmol, 3.20 eq.) and Et<sub>3</sub>N (3.89 mL, 2.84 g, 28.1 mmol, 1.28 eq.) was stirred for 6 h at 80 °C. All volatiles

were evaporated in HV to afford an orange solid which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with H<sub>2</sub>O (3 × 30 mL). The organic layer was dried over MgSO<sub>4</sub> followed by purification by column chromatography (SiO<sub>2</sub>, d × h: 6 × 30 cm, cyclohexane:ethyl acetate (8:1)) to afford the product (570 mg, 2.56 mmol, 12%) as a colorless solid.

C<sub>15</sub>H<sub>10</sub>O<sub>2</sub> (222.24 g/mol):

**MP:** 134-137 °C.

**TLC:** R<sub>f</sub> = 0.31 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (8:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.81 (s, 1H, C=CH), 7.74-7.68 (m, 3H, ar-*H*), 7.55-7.51 (m, 2H, ar-*H*), 7.48-7.34 (m, 4H, ar-*H*), 7.32-7.28 (m, 1H, ar-*H*).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 160.8, 153.7, 140.1, 134.9, 131.6, 129.1, 128.7, 128.7, 128.5, 128.1, 124.7, 119.9, 116.6.

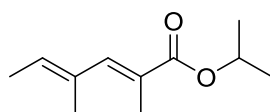
**MS** (EI, 70 eV, 200 °C) *m/z* (%): 223.0 (17), 222.0 (100), 195.1 (12), 194.1 (77), 166.1 (11), 165.1 (72), 164.1 (11), 139.1 (12), 97.1 (12), 82.1 (20).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 36.07 min.

**HPLC:** *Daicel* Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min; T = 20 °C, 208 nm, t<sub>R</sub> = 35.7 min.

Obtained data are in accordance with literature data.<sup>[141]</sup>

### Isopropyl (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoate (3.49)



To a solution of (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoic acid (300 mg, 2.14 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), oxalyl chloride (184 μL, 2.14 mmol, 1.00 eq.) and DMF (20 μL) were added dropwise in this order at 0 °C. The reaction mixture was stirred for 2 h at room temperature and isopropanol (1.3 mL, 21.4 mmol, 10.0 eq.) and triethylamine (600 μL, 4.28 mmol, 2.00 eq.) were added to the mixture at 0 °C. The reaction mixture was stirred at room temperature overnight. H<sub>2</sub>O (10 mL) was added, the biphasic mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL) and dried over MgSO<sub>4</sub>. All volatiles were evaporated under reduced pressure and purification by a column chromatography (SiO<sub>2</sub>, d × h: 3.5 × 10 cm, pentane:Et<sub>2</sub>O (20:1)) afforded the product (218 mg, 1.18 mmol, 55%) as a colorless oil.

$C_{11}H_{18}O_2$  (182.13 g/mol):

**TLC:**  $R_f$  = 0.35 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (20:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.03 (s, 1H, C=CH), 5.64 (q,  $J$  = 7.0 Hz, 1H, C=CH), 4.99 (sept,  $J$  = 6.3 Hz, 1H, OCH), 1.92 (s, 3H, CH<sub>3</sub>), 1.77 (s, 3H, CH<sub>3</sub>), 1.68 (d,  $J$  = 7.0 Hz, 3H, CH<sub>3</sub>), 1.20 (d,  $J$  = 6.3 Hz, 6H, CH<sub>3</sub>).

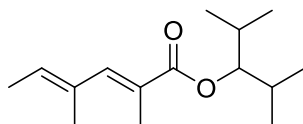
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 168.8 (s, C=O), 142.6 (s, C=CH), 133.1 (s, C=CH), 130.6 (s, C=CH), 125.3 (s, C=CH), 67.7 (s, OCH), 21.9 (s, CH<sub>3</sub>), 16.0 (s, CH<sub>3</sub>), 14.0 (s, CH<sub>3</sub>), 14.0 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 2964 (w), 2934 (w), 1702 (s), 1352 (m), 1245 (s), 1181 (s), 820 (w), 744 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 182.1 (6), 140.1 (37), 125-1 (100), 123.1 (18), 95.1 (33), 79.1 (26), 67.0 (12), 55.0 (10), 43.0 (21), 41.0 (19).

**GC-MS** (Restek Rtx-5MS (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 100 kPa He (50 °C – 2 min – 30 °C/min – 250 °C – 5 min):  $t_R$  = 6.6 min.

### 2,4-Dimethylpentan-3-yl (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoate (3.51)



To a solution of (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoic acid (300 mg, 2.14 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), oxalyl chloride (184  $\mu$ L, 2.14 mmol, 1.00 eq.) and DMF (20  $\mu$ L) were added dropwise in this order at 0 °C. The reaction mixture was stirred for 2 h at room temperature and 2,4-dimethylpentan-3-ol (2.27 mL, 21.4 mmol, 10.0 eq.) and triethylamine (600  $\mu$ L, 4.28 mmol, 2.00 eq.) were added to the mixture at 0 °C. The reaction mixture was stirred at room temperature overnight. H<sub>2</sub>O (10 mL) was added, the biphasic mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL) and dried over MgSO<sub>4</sub>. All volatiles were evaporated under reduced pressure and purification by a column chromatography (SiO<sub>2</sub>, d  $\times$  h: 3.5  $\times$  10 cm, pentane:Et<sub>2</sub>O (100:1)) afforded the product (327 mg, 1.37 mmol, 64%) as a colorless oil.

$C_{15}H_{26}O_2$  (238.37 g/mol):

**TLC:**  $R_f$  = 0.25 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (100:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.07 (s, 1H, C=CH), 5.66 (q,  $J$  = 7.0 Hz, 1H, C=CH), 4.60 (t,  $J$  = 6.1 Hz, 1H, OCH), 1.95 (s, 3H, CH<sub>3</sub>), 1.93-1.81 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.78 (s, 3H, CH<sub>3</sub>), 1.68 (d,  $J$  = 7.0 Hz, 3H, CH<sub>3</sub>), 0.82 (dd,  $J$  = 6.8, 3.2 Hz, 12H, CH<sub>3</sub>).

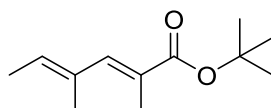
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 169.3 (s,  $\text{C}=\text{O}$ ), 142.7 (s,  $\text{C}=\text{CH}$ ), 133.2 (s,  $\text{C}=\text{CH}$ ), 130.8 (s,  $\text{C}=\text{CH}$ ), 125.0 (s,  $\text{C}=\text{CH}$ ), 82.6 (s,  $\text{OCH}$ ), 29.6 (s,  $\text{CH}_3$ ), 19.6 (s,  $\text{CH}_3$ ), 17.3 (s,  $\text{CH}_3$ ), 16.0 (s,  $\text{CH}$ ), 14.1 (s,  $\text{CH}_3$ ), 14.0 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2978 (w), 2924 (w), 1700 (s), 1356 (m), 1251 (s), 1143 (s), 828 (w), 704 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 238.4 (6), 141.4 (11), 140.4 (90), 125.3 (100), 123.3 (89), 95.2 (67), 83.2 (15), 79.2 (13), 67.1 (21), 57.1 (28), 55.0 (19), 43.0 (27), 41.0 (24).

**GC-MS** (Restek Rtx-5MS (30 m  $\times$  0.25 mm  $\times$  0.25 m) 100 kPa He (50 °C – 2 min – 30 °C/min – 250 °C – 5 min):  $t_R$  = 7.9 min.

***tert*-Butyl (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoate (3.50)**



To a solution of (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienoic acid (300 mg, 2.14 mmol, 1.00 eq.) in  $\text{CH}_2\text{Cl}_2$  (5 mL), oxalyl chloride (184  $\mu\text{L}$ , 2.14 mmol, 1.00 eq.) and DMF (20  $\mu\text{L}$ ) were added dropwise in this order at 0 °C. The reaction mixture was stirred for 2 h at room temperature and *tert*-butanol (1.70 mL, 21.4 mmol, 10.0 eq.) and triethylamine (600  $\mu\text{L}$ , 4.28 mmol, 2.00 eq.) were added to the mixture at 0 °C. The reaction mixture was stirred overnight at room temperature.  $\text{H}_2\text{O}$  (10 mL) was added, the biphasic mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  10 mL) and dried over  $\text{MgSO}_4$ . All volatiles were evaporated under reduced pressure and purification by a column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 3.5  $\times$  10 cm, pentane: $\text{Et}_2\text{O}$  (50:1)) afforded the product (145 mg, 739  $\mu\text{mol}$ , 35%) as a colorless oil.

$\text{C}_{12}\text{H}_{20}\text{O}_2$  (196.29 g/mol):

**TLC**:  $R_f$  = 0.65 ( $\text{SiO}_2$ , pentane: $\text{Et}_2\text{O}$  (30:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 6.96 (s, 1H,  $\text{C}=\text{CH}$ ), 5.61 (q,  $J$  = 7.0 Hz, 1H,  $\text{CH}$ ), 1.88 (s, 3H,  $\text{CH}_3$ ), 1.76 (s, 3H,  $\text{CH}_3$ ), 1.67 (d,  $J$  = 7.0 Hz, 3H,  $\text{CH}_3$ ), 1.42 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 168.6 (s,  $\text{C}=\text{O}$ ), 142.1 (s,  $\text{C}=\text{CH}$ ), 133.1 (s,  $\text{C}=\text{CH}$ ), 130.1 (s,  $\text{C}=\text{CH}$ ), 126.5 (s,  $\text{C}=\text{CH}$ ), 80.0 (s,  $\text{OC}(\text{CH}_3)_3$ ), 28.1 (s,  $\text{OC}(\text{CH}_3)_3$ ), 16.0 (s,  $\text{CH}_3$ ), 14.0 (s,  $\text{CH}_3$ ), 14.0 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2977 (w), 2929 (w), 1699 (s), 1330 (m), 1268 (s), 1252 (s), 1119 (s), 822 (w), 701 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 196.3 (6), 140.2 (37), 125.2 (100), 123.2 (19), 95.1 (31), 79.0 (11), 67.0 (10), 57.0 (30), 41.0 (37).

**GC-MS** (Restek Rtx-5MS (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 100 kPa He (50 °C – 2 min – 30 °C/min – 250 °C – 5 min):  $t_R$  = 6.9 min.

### 8.3.2 Hydrogenation products of $\alpha,\beta$ -unsaturated carboxylic esters

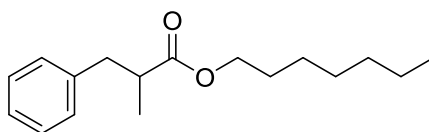
#### General procedure: Iridium-catalyzed hydrogenation GP7

Typical procedure for Ir-catalyzed hydrogenation: Iridium catalyst (1.0 mol%) was added to a solution of substrate (0.10 mmol), in  $\text{CH}_2\text{Cl}_2$  (0.5 mL). The reaction vial was equipped with a magnetic stir bar and placed in an autoclave that was pressurized to 50 bar with  $\text{H}_2$ . The reaction mixture was stirred at 800 rpm for the given time, after this time, hydrogen was released and the solvent removed under reduced pressure. The mixture was filtered through a plug of silica gel (d  $\times$  h: 0.5  $\times$  2.0 cm) using a mixture of pentane: $\text{Et}_2\text{O}$  (1:1, 5.0 mL). Evaporation of the solvent afforded the analytically pure hydrogenation product.

#### General procedure: $\text{Pd}(\text{OH})_2/\text{C}$ catalyzed hydrogenation GP8

Typical procedure for  $\text{Pd}(\text{OH})_2/\text{C}$  catalyzed hydrogenation:  $\text{Pd}(\text{OH})_2/\text{C}$  (15 mg, 20 wt%) was added to a solution of substrate (0.20 mmol), in  $\text{CH}_2\text{Cl}_2$  (0.8 mL). The reaction vial was equipped with a magnetic stir bar and placed in an autoclave that was pressurized to 50 bar with  $\text{H}_2$ . The reaction mixture was stirred at 800 rpm for 16 h, after this time, hydrogen was released and the reaction mixture was filtered through a syringe filter. Evaporation of the solvent afforded the analytically pure hydrogenation product.

#### Heptyl 2-methyl-3-phenylpropanoate (3.9)



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$\text{C}_{17}\text{H}_{26}\text{O}_2$  (262.39 g/mol):

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm = 7.31-7.23 (m, 2H, ar-*H*), 7.23-7.13 (m, 3H, ar-*H*), 4.02 (t,  $^3J_{\text{HH}}$  = 6.7 Hz, 2H,  $\text{OCH}_2\text{CH}_2$ ), 3.02 (dd,  $^2J_{\text{HH}}$  = 12.9 Hz,  $^3J_{\text{HH}}$  = 6.5 Hz, 1H, ar- $\text{CH}_2$ ), 2.79-



2.62 (m, 2H, ar-CH<sub>2</sub>, ar-CH<sub>2</sub>CH), 1.61–1.48 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.35–1.21 (m, 8H, alkyl-H), 1.15 (d, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz, 3H, CHCH<sub>3</sub>), 0.88 (t, <sup>3</sup>J<sub>HH</sub> = 6.5 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ/ppm = 176.4 (s, C=O), 139.6 (s, ar-C), 129.25 (s, ar-C), 128.5 (s, ar-C), 126.45 (s, ar-C), 64.7 (s, OCH<sub>2</sub>), 41.7 (s, CH), 40.0 (CH<sub>2</sub>-ar), 31.9 (s, CH<sub>2</sub>), 29.1 (s, CH<sub>2</sub>), 28.8 (s, CH<sub>2</sub>), 26.0 (s, CH<sub>2</sub>), 22.8 (s, CH<sub>2</sub>), 17.0 (s, CH<sub>3</sub>), 14.3 (s, CH<sub>3</sub>).

MS (EI, 70 eV, 200 °C) *m/z* (%): 262.2 (11), 164.2 (22), 119.1 (14), 118.1 (52), 91.0 (100), 57.0 (16).

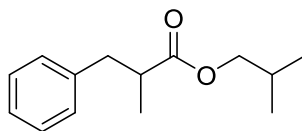
IR (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3028 (w), 2955 (m), 2928 (m), 2856 (m), 1731 (s), 1497 (w), 1454 (m), 1200 (m), 1163 (s), 1117 (m), 1030 (m), 742 (m), 698 (s), 669 (m).

EA (C<sub>17</sub>H<sub>26</sub>O<sub>2</sub>): calculated: C 77.82, H 9.99; found: C 77.95, H 9.90.

GC: (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): *t<sub>R</sub>* = 23.56 min.

HPLC: Daicel Chiralcel OJ (0.46 cm × 25 cm, heptane, 0.5 mL/min; T = 25 °C, 220 nm, *t<sub>R</sub>* = 14.9 min (*R*) and 16.5 min (*S*)).

### Isobutyl 2-methyl-3-phenylpropanoate (3.8)



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

C<sub>14</sub>H<sub>20</sub>O<sub>2</sub> (220.31 g/mol):

TLC: *R<sub>f</sub>* = 0.47 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (50:1), UV).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.30–7.26 (m, 2H, ar-H), 7.22–7.16 (m, 3H, ar-H), 3.82 (d, <sup>3</sup>J<sub>HH</sub> = 6.6 Hz, 2H, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 3.04 (dd, <sup>2</sup>J<sub>HH</sub> = 13.1 Hz, <sup>3</sup>J<sub>HH</sub> = 6.8 Hz, 1H, arCH<sub>2</sub>CHCH<sub>3</sub>), 2.80–2.65 (m, 2H, arCH<sub>2</sub>CHCH<sub>3</sub> and arCH<sub>2</sub>CHCH<sub>3</sub>), 1.92–1.82 (m, 1H, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.17 (t, <sup>3</sup>J<sub>HH</sub> = 6.8 Hz, 3H, arCH<sub>2</sub>CHCH<sub>3</sub>), 0.88 (d, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz, 6H, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ/ppm = 176.3 (s, C=O), 139.6 (s, ar-*q*C), 129.1 (s, ar-C), 128.5 (s, ar-C), 126.4 (s, ar-C), 70.6 (s, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 41.8 (s, arCH<sub>2</sub>CHCH<sub>3</sub>), 40.0 (s, ar-CH<sub>2</sub>), 27.9 (s, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 19.2 (s, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 17.0 (s, arCH<sub>2</sub>CHCH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3028 (w), 2962 (m), 2937 (m), 1732 (s), 1497 (m), 1454 (m), 1394 (w), 1379 (m), 1367 (m), 1356 (m), 1282 (m), 1202 (m), 1163 (s), 1117 (m), 1089 (m), 1040 (m), 993 (m), 744 (m), 700 (s), 661 (m).

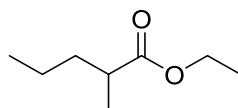
**MS** (EI, 70 eV, RT)  $m/z$  (%): 220.2 (12), 164.1 (19), 147.1 (11), 119.1 (17), 118.1 (23), 91.1 (100).

**EA** ( $\text{C}_{14}\text{H}_{20}\text{O}_2$ ): calc.: C 76.33, H 9.15; found: C 76.32, H 9.18.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100  $^{\circ}\text{C}$  – 2 min – 7  $^{\circ}\text{C}/\text{min}$  – 250  $^{\circ}\text{C}$  – 10 min):  $t_{\text{R}}$  = 29.84 min.

**HPLC**: Daicel Chiralpak AD-H (0.46 cm  $\times$  25 cm, heptane, 0.5 mL/min, 25  $^{\circ}\text{C}$ , 208 nm):  $t_{\text{R}}$  = 27.9 min (*S*) and 29.8 min (*R*).

### Ethyl 2-methylpentanoate (3.29)



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$\text{C}_8\text{H}_{16}\text{O}_2$  (144.21 g/mol):

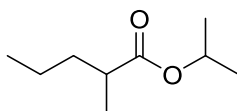
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 4.05 (q,  $J$  = 7.1 Hz, 2H,  $\text{OCH}_2$ ), 2.40-2.31 (m, 1H, CH), 1.36-1.21 (m, 4H,  $2 \times \text{CH}_2$ ), 1.18 (t,  $J$  = 7.1 Hz, 3H,  $\text{CH}_3$ ), 1.07 (d,  $J$  = 7.0 Hz, 3H,  $\text{CH}_3$ ), 0.83 (t,  $J$  = 7.2 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 177.1 (s,  $\text{C}=\text{O}$ ), 60.2 (s,  $\text{OCH}_2$ ), 39.5 (s, CH), 36.1 (s,  $\text{CH}_2$ ), 20.5 (s,  $\text{CH}_2$ ), 17.2 (s,  $\text{CH}_3$ ), 14.4 (s,  $\text{CH}_2$ ), 14.1 (s,  $\text{CH}_2$ ).

**MS** (EI, 70 eV, 200  $^{\circ}\text{C}$ )  $m/z$  (%): 115.1 (14), 102.1 (100), 99.1 (26), 87.1 (13), 74.1 (60), 73.1 (12), 71.1 (61), 55.1 (12).

**GC** (Chiraldex  $\gamma$ -cyclodextrin TFA G-TA (30 m  $\times$  0.25 mm  $\times$  0.12  $\mu\text{m}$ ), 60 kPa  $\text{H}_2$  (30  $^{\circ}\text{C}$  – 50 min – 10  $^{\circ}\text{C}/\text{min}$  – 160  $^{\circ}\text{C}$  – 10 min):  $t_{\text{R}}$  = 41.0 min (–), 43.6 (+) min.

Compound available from different commercial sources (CAS: 39255-32-8).

**Isopropyl 2-methylpentanoate (3.30)**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_9H_{18}O_2$  (158.24 g/mol):

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 4.99 (sept,  $^3J_{HH}$  = 6.2 Hz, 1H,  $CO_2CH(CH_3)_2$ ), 2.42-2.30 (m, 1H,  $CHCH_3$ ), 1.62 (m, 1H,  $CHCH_2$ ), 1.41-1.24 (m, 3H,  $CHCH_2$  and  $CHCH_2CH_2$ ), 1.21 (d,  $^3J_{HH}$  = 6.3 Hz, 6H,  $CO_2CH(CH_3)_2$ ), 1.10 (d,  $^3J_{HH}$  = 7.0 Hz, 3H,  $CHCH_3$ ), 0.89 (t,  $^3J_{HH}$  = 7.2 Hz, 3H,  $CH_3CH_2$ ).

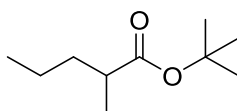
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 176.7 (s,  $CO_2CH(CH_3)_2$ ), 67.3 (s,  $CO_2CH(CH_3)_2$ ), 39.7 (s, CH), 36.2 (s,  $CH_2CH$ ), 22.0 (s,  $CO_2CH(CH_3)_2$ ), 22.0 (s,  $CO_2CH(CH_3)_2$ ), 20.6 (s,  $CH_3CH_2$ ), 17.2 (s,  $CH_3$ ), 14.2 (s,  $CH_3$ ).

**IR** (ATR):  $\tilde{\nu}/cm^{-1}$  = 2975 (m), 2968 (m), 2934 (m), 2875 (w), 1728 (s), 1455 (m), 1374 (m), 1273 (w), 1253 (w), 1235 (w), 1181 (s), 1152 (m), 1108 (s), 1083 (m), 950 (w), 918 (w), 667 (s).

**MS** (EI, 70 eV, Inlet 150 °C)  $m/z$  (%): 117.1 (12), 116.1 (20), 99.1 (25), 74.1 (40), 44.9 (45), 43.1 (100), 41.0 (17).

**EA** ( $C_9H_{18}O_2$ ): calc.: C 68.31, H 11.47; found: C 68.18, H 11.26.

**GC** (*Chiraldex*  $\gamma$ -cyclodextrin TFA G-TA (30 m  $\times$  0.25 mm  $\times$  0.12  $\mu$ m), 60 kPa  $H_2$  (45 °C – 25 min – 20 °C/min – 160 °C – 5 min):  $t_R$  = 17.8 min (–), 19.2 min (+).

**tert-Butyl 2-methylpentanoate (3.31)**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{10}H_{20}O_2$  (172.27 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 2.41-2.23 (m, 1H,  $\text{CHCH}_3$ ), 1.71-1.51 (m, 1H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.44 (s, 9H,  $\text{CO}_2\text{C}(\text{CH}_3)_3$ ), 1.39-1.23 (m, 3H,  $\text{CH}_2\text{CH}_2\text{CH}_3$  and  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.09 (d,  $^3J_{\text{HH}} = 7.0$  Hz, 3H,  $\text{CHCH}_3$ ), 0.90 (t,  $^3J_{\text{HH}} = 7.1$  Hz, 3H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 176.6 (s,  $\text{C}=\text{O}$ ), 79.9 (s,  $\text{CO}_2\text{C}(\text{CH}_3)_3$ ), 40.5 (s, CH), 36.3 (s,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 28.3 (s,  $\text{CO}_2\text{C}(\text{CH}_3)_3$ ), 20.6 (s,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 17.4 (s,  $\text{CH}_3$ ), 14.3 (s,  $\text{CH}_3$ ).

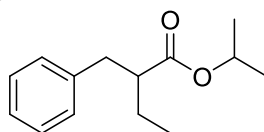
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2964 (m), 2908 (w), 2867 (m), 1728 (s), 1455 (m), 1391 (w), 1366 (m), 1255 (m), 1143 (s), 1084 (m), 849 (m).

**MS** (EI, 70 eV, Inlet 150 °C)  $m/z$  (%): 99.1 (18)  $[\text{M}-\text{O}(t\text{-Bu})]^+$ , 71.1 (26)  $[\text{M}-\text{CO}_2(t\text{-Bu})]^+$ , 57.1 (100), 43.1 (11), 41.0 (17).

**EA** ( $\text{C}_{10}\text{H}_{20}\text{O}_2$ ): calc.: C 69.72, H 11.70; found: C 69.77, H 11.49.

**GC** (*ChiralDEX*  $\gamma$ -cyclodextrin TFA G-TA (30 m  $\times$  0.25 mm  $\times$  0.12  $\mu\text{m}$ ), 60 kPa  $\text{H}_2$  (45 °C – 25 min – 20 °C/min – 160 °C – 5 min),  $t_{\text{R}}$  = 16.8 min (+), 17.7 min (–).

### Isopropyl 2-benzylbutanoate (3.15)



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to procedure **GP8**.

$\text{C}_{14}\text{H}_{20}\text{O}_2$  (220.31 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.29-7.24 (m, 2H, ar-*H*), 7.20-7.16 (m, 3H, ar-*H*), 4.95 (sept,  $^3J_{\text{HH}} = 6.3$  Hz, 1H,  $\text{OCH}(\text{CH}_3)_2$ ), 2.90 (dd,  $^2J_{\text{HH}} = 13.6$  Hz,  $^3J_{\text{HH}} = 8.7$  Hz, 1H, ar- $\text{CH}_2$ ), 2.74 (dd,  $^2J_{\text{HH}} = 13.6$  Hz,  $^3J_{\text{HH}} = 6.6$  Hz, 1H, ar- $\text{CH}_2$ ), 2.57-2.51 (m, 1H,  $\text{CHCH}_2$ ), 1.72-1.49 (m, 2H,  $\text{CHCH}_2$ ), 1.17 (d,  $^3J_{\text{HH}} = 6.3$  Hz, 3H,  $\text{OCH}(\text{CH}_3)_2$ ), 1.06 (d,  $^3J_{\text{HH}} = 6.3$  Hz, 3H,  $\text{OCH}(\text{CH}_3)_2$ ), 0.92 (t,  $^3J_{\text{HH}} = 7.4$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 175.3 (s,  $\text{C}=\text{O}$ ), 139.8 (s, ar- $q\text{-C}$ ), 129.2 (s, ar- $\text{C}$ ), 128.5 (s, ar- $\text{C}$ ), 126.4 (s, ar- $\text{C}$ ), 67.5 (s,  $\text{OCH}(\text{CH}_3)_2$ ), 49.6 (s,  $\text{CHCO}$ ), 38.5 (s, ar- $\text{CH}_2$ ), 25.5 (s,  $\text{CH}_2\text{CH}_3$ ), 22.1 (s,  $\text{CH}(\text{CH}_3)_2$ ), 21.9 (s,  $\text{CH}(\text{CH}_3)_2$ ), 11.9 (s,  $\text{CH}_2\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3031 (w), 2968 (m), 2933 (m), 2876 (w), 1726 (s), 1494 (m), 1454 (m), 1410 (m), 1371 (m), 1231 (w), 1200 (m), 1165 (m), 1143 (m), 1107 (s), 1074 (m), 1024 (w), 1011 (m), 970 (m), 959 (m), 827 (m), 698 (s).

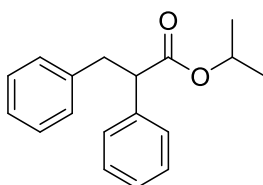
**MS** (EI, 70 eV, RT)  $m/z$  (%): 220.1 (11), 178.1 (22), 133.1 (16), 132.1 (17), 131.1 (10), 92 (11), 91 (100).

**EA** ( $\text{C}_{14}\text{H}_{20}\text{O}_2$ ): calc.: C 76.33, H 9.15; found: C 75.98, H 9.20.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100  $^{\circ}\text{C}$  – 2 min – 7  $^{\circ}\text{C}/\text{min}$  – 250  $^{\circ}\text{C}$  – 10 min):  $t_{\text{R}}$  = 16.66 min.

**HPLC**: Daicel Chiralcel OJ (0.46 cm  $\times$  25 cm, heptane, 0.5 mL/min, 25  $^{\circ}\text{C}$ , 208 nm):  $t_{\text{R}}$  = 15.6 min (–),  $t_{\text{R}}$  = 18.1 min (+).

### Isopropyl 2,3-diphenylpropanoate (3.21)



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$\text{C}_{18}\text{H}_{20}\text{O}_2$  (268.36 g/mol):

**TLC**:  $R_f$  = 0.50 ( $\text{SiO}_2$ , pentane:Et<sub>2</sub>O (20:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.27–7.19 (m, 4H, ar-*H*), 7.19–7.12 (m, 3H, ar-*H*), 7.11–7.03 (m, 3H, ar-*H*), 4.84 (sept,  $^3J_{\text{HH}}$  = 6.3 Hz, 1H, OCH(CH<sub>3</sub>)<sub>2</sub>), 3.73 (dd,  $^3J_{\text{HH}}$  = 9.2 Hz,  $^3J_{\text{HH}}$  = 6.4 Hz, 1H, ar-*CH*), 3.31 (dd,  $^2J_{\text{HH}}$  = 13.7 Hz,  $^3J_{\text{HH}}$  = 9.3 Hz, 1H, ar-*CH*<sub>2</sub>), 2.93 (dd,  $^2J_{\text{HH}}$  = 13.7 Hz,  $^3J_{\text{HH}}$  = 6.4 Hz, 1H, ar-*CH*<sub>2</sub>), 0.99 (d,  $^3J_{\text{HH}}$  = 6.3 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 173.0 (s, C=O), 139.3 (s, ar-C), 139.1 (s, ar-C), 129.2 (s, ar-C), 128.7 (s, ar-C), 128.4 (s, ar-C), 128.1 (s, ar-C), 127.4 (s, ar-C), 126.5 (s, ar-C), 68.2 (s, OCH(CH<sub>3</sub>)<sub>2</sub>), 54.0 (s, CH), 40.1 (s, CH<sub>2</sub>), 21.8 (s, OCH(CH<sub>3</sub>)<sub>2</sub>), 21.7 (s, OCH(CH<sub>3</sub>)<sub>2</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3028 (w), 2978 (w), 2965 (w), 2928 (w), 1724 (s), 1601 (w), 1495 (m), 1453 (m), 1372 (m), 1212 (m), 1162 (m), 1104 (s), 1071 (m), 1030 (m), 745 (m), 696 (s).

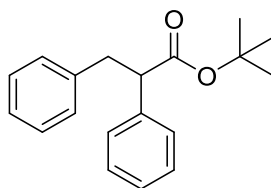
**MS** (EI, 70 eV, RT)  $m/z$  (%): 268.2 (23), 182.1 (11), 181.1 (76), 180.1 (10), 166.3 (13), 165.2 (11), 103.1 (17), 91.1 (100), 77.1 (10), 43.1 (10).

**EA** ( $C_{18}H_{20}O_2$ ): calc.: C 80.56, H 7.51; found: C 80.41, H 7.76.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100  $^{\circ}$ C – 2 min – 7  $^{\circ}$ C/min – 250  $^{\circ}$ C – 10 min):  $t_R$  = 24.49 min.

**HPLC**: Daicel, Chiralpak IC (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min, 25  $^{\circ}$ C, 220 nm):  $t_R$  = 9.42 min (+) and 9.98 min (–).

***tert*-Butyl 2,3-diphenylpropanoate (3.22)**



The enantiomerically enriched product was obtained as a colorless solid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{19}H_{22}O_2$  (282.38 g/mol):

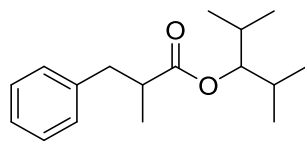
**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 7.35-7.28 (m, 4H, ar-*H*), 7.28-7.22 (m, 3H, ar-*H*), 7.20-7.13 (m, 3H, ar-*H*), 3.77 (ddd,  $J$  = 9.3, 6.4, 1.0 Hz, 1H, CH), 3.36 (dd,  $J$  = 13.7, 9.2 Hz, 1H), 2.99 (dd,  $J$  = 13.7, 6.4 Hz, 1H,  $CH_2$ ), 1.32 (s, 9H,  $C(CH_3)_3$ ).

**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 172.7 (s, C=O), 139.5 (s, ar- $qC$ ), 139.4 (s, ar- $qC$ ), 129.2 (s, ar- $C$ ), 128.6 (s, ar- $C$ ), 128.3 (s, ar- $C$ ), 128.0 (s, ar- $C$ ), 127.2 (s, ar- $C$ ), 126.4 (s, ar- $C$ ), 80.9 (s,  $OC(CH_3)_3$ ), 54.6 (s, CH), 40.1 (s,  $CH_2$ ), 28.0 (s,  $CH_3$ ).

**IR** (ATR):  $\tilde{\nu}/cm^{-1}$  = 3031 (w), 2980 (w), 2928 (w), 2852 (w), 1716 (s), 1599 (w), 1494 (w), 1454 (m), 1391 (m), 1367 (m), 1347 (m), 1235 (m), 1146 (s), 1079 (w), 843 (m), 745 (s), 697 (s), 547 (s).

**MS** (EI, 70 eV, RT)  $m/z$  (%): 282.2 (1), 227.1 (8), 226.1 (48), 182.1 (13), 181.1 (60), 166.1 (12), 165.1 (11), 103.1 (17), 91.1 (50), 77.1 (13), 57.1 (100), 41.1 (19).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100  $^{\circ}$ C – 2 min – 7  $^{\circ}$ C/min – 250  $^{\circ}$ C – 15 min):  $t_R$  = 24.51 min.

**2,4-Dimethylpentan-3-yl 2-methyl-3-phenylpropanoate**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{17}H_{26}O_2$  (262.39 g/mol):

**TLC:**  $R_f$  = 0.44 ( $SiO_2$ , cyclohexane:ethyl acetate (50:1), UV).

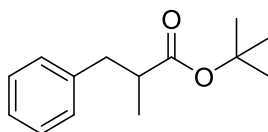
**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 7.36-7.29 (m, 2H, ar-*H*), 7.28-7.21 (m, 2H, ar-*H*), 4.62 (t,  $J$  = 6.1 Hz, 1H,  $CH(CH)_2$ ), 3.14 (dd,  $J$  = 13.5, 7.0 Hz, 1H,  $C_6H_5CH_2$ ), 2.89-2.80 (m, 1H,  $CH(CH)_2$ ), 2.70 (dd,  $J$  = 13.5, 8.0 Hz, 1H,  $C_6H_5CH_2$ ), 1.98-1.82 (m, 2H,  $CH(CH)_2$ ), 1.24 (d,  $J$  = 7.0 Hz, 3H,  $CHCH_3$ ), 0.90 (dd,  $J$  = 9.4, 6.8 Hz, 6H,  $CH(CH(CH_3)_2)_2$ ), 0.80 (dd,  $J$  = 10.8, 6.8 Hz, 6H,  $CH(CH(CH_3)_2)_2$ ).

**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 176.2 (s,  $CO_2$ ), 139.7 (s, ar-C), 129.2 (s, ar-C), 128.4 (s, ar-C), 126.3 (s, ar-C), 82.5 (s,  $CH(CH)_2$ ), 42.0 (s,  $CHCH_2$ ), 39 (s,  $CH_2$ ), 29.5  $CH(CH)_2$ , 29.5 (s,  $CH(CH)_2$ ), 19.7 (s,  $CH_3$ ), 19.5 (s,  $CH_3$ ), 17.5 (s,  $CH_3$ ), 17.3 (s,  $CH_3$ ), 17.2 (s,  $CH_3$ ).

**IR** (ATR):  $\tilde{\nu}/cm^{-1}$  = 3029 (w), 2967 (m), 2935 (m), 2877 (w), 1731 (s), 1496 (w), 1463 (m), 1371 (m), 1339 (w), 1278 (w), 1249 (w), 1209 (m), 1168 (s), 1131 (m), 1098 (m), 1031 (m), 999 (w), 964 (w), 902 (w), 774 (m), 699 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 164.1 (38), 147.1 (53), 119.1 (72), 118.1 (15), 99.1 (18), 98.1 (19), 91.1 (100), 83.1 (12), 57.1 (73), 43.1 (17).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min):  $t_R$  = 21.24 min.

**tert-Butyl 2-methyl-3-phenylpropanoate**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

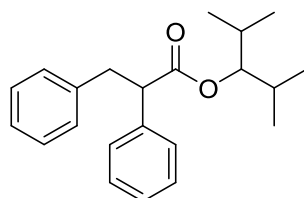
$C_{14}H_{20}O_2$  (220.31 g/mol):

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta/ppm = 7.31-7.23$  (m, 2H, ar-*H*), 7.24-7.15 (m, 3H, ar-*H*), 3.03-2.88 (m, 1H, *CH*), 2.66-2.56 (m, 2H,  $CH_2$ ), 1.38 (s, 9H,  $C(CH_3)_3$ ), 1.12 (d,  $J = 6.5$  Hz, 3H,  $CH_3$ ).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta/ppm = 175.7$  (s,  $C=O$ ), 139.9 (s, ar- $qC$ ), 129.3 (s, ar- $C$ ), 128.4 (s, ar- $C$ ), 126.3 (s, ar- $C$ ), 80.2 (s,  $OC(CH_3)_3$ ), 42.5 (s,  $CH$ ), 40.0 (s,  $CH_2$ ), 28.2 (s,  $OC(CH_3)_3$ ), 17.2 (s,  $CH_3$ ).

Obtained data are in accordance with literature data.<sup>[142]</sup>

### 2,4-Dimethylpentan-3-yl 2,3-diphenylpropanoate (3.23)



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{22}H_{28}O_2$  (324.46 g/mol):

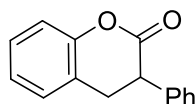
$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta/ppm = 7.40-7.11$  (m, 10H, ar-*H*), 4.49 (t,  $J = 6.1$  Hz, 1H,  $CO_2CH$ ), 3.89 (dd,  $J = 9.2, 6.3$  Hz, 1H,  $CH_2$ ), 3.46 (dd,  $J = 13.7, 9.3$  Hz, 1H,  $CH_2$ ), 3.04 (dd,  $J = 13.7, 6.3$  Hz, 1H,  $CH$ ), 1.83-1.66 (m,  $J = 6.4$  Hz, 2H,  $OC((CH)_2CH_3)_2$ ), 0.66 (d,  $J = 6.8$  Hz, 3H,  $OC((CH)_2CH_3)_2$ ), 0.65-0.54 (m, 9H,  $OC((CH)_2CH_3)_2$ ).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta/ppm = 173.5$  (s,  $CO_2$ ), 139.5 (s, ar- $C$ ), 139.3 (s, ar- $C$ ), 129.3 (s, ar- $C$ ), 128.7 (s, ar- $C$ ), 128.5 (s, ar- $C$ ), 128.3 (s, ar- $C$ ), 127.5 (s, ar- $C$ ), 126.5 (s, ar- $C$ ), 83.2 (s,  $OC((CH)_2CH_3)_2$ ), 54.1 (s,  $CH$ ), 39.6 (s,  $CH_2$ ), 29.4 (s,  $CH$ ), 29.1 (s,  $CH$ ), 19.2 (s,  $CH_3$ ), 19.3 (s,  $CH_3$ ), 17.4 (s,  $CH_3$ ), 16.9 (s,  $CH_3$ ).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu m$ ) 60 kPa He (100  $^{\circ}C$  – 2 min – 7  $^{\circ}C/min$  – 250  $^{\circ}C$  – 10 min):  $t_R = 29.84$  min.

**HPLC**: Daicel Chiralpak AD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 99:01, 0.5 mL/min;  $T = 20$   $^{\circ}C$ , 208 nm,  $t_R = 12.6$  min and 13.9 min.



**3-Phenylchroman-2-one**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

C<sub>15</sub>H<sub>12</sub>O<sub>2</sub> (224.26 g/mol):

**MP:** 115-116 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.24-7.41 (m, 6H, ar-*H*), 7.20-7.26 (m, 1H, ar-*H*), 7.09-7.18 (m, 2H, ar-*H*), 4.01 (dd, *J* = 11.2, 6.2 Hz, 1H, CH), 3.38 (dd, *J* = 15.6, 11.2 Hz, 1H, CH<sub>2</sub>), 3.25 (dd, *J* = 15.6, 6.2 Hz, 1H, CH<sub>2</sub>).

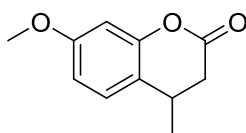
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ/ppm = 151.7 (s, CO<sub>2</sub>), 136.5 (s, ar-C), 128.9 (s, ar-C), 128.6 (s, ar-C), 128.2 (s, ar-C), 128.0 (s, ar-C), 127.8 (s, ar-C), 124.6 (s, ar-C), 122.6 (s, ar-C), 116.8 (s, ar-C), 45.6 (s, CH), 31.8 (s, CH<sub>2</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 225.1 (17), 224.1 (100), 197.1 (14), 196.1 (93), 195.1 (62), 181.1 (17), 179.1 (19), 178.1 (14), 177.1 (12), 167.1 (27), 165.1 (22), 152.1 (19), 118.1 (28), 90.1 (23), 89.1 (26), 77.1 (12), 63.1 (10), 51.0 (11).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 29.94 min.

**HPLC:** *Daicel* Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min; T = 20 °C, 208 nm, t<sub>R</sub> = 49.1 min and 57.7 min.

Obtained data are in accordance with literature data.<sup>[141]</sup>

**7-Methoxy-4-methylchroman-2-one**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

C<sub>11</sub>H<sub>12</sub>O<sub>3</sub> (192.21 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.10 (d,  $J$  = 8.4 Hz, 1H, ar-*H*), 6.66 (dd,  $J$  = 8.4, 2.4 Hz, 1H, ar-*H*), 6.60 (d,  $J$  = 2.4 Hz, 1H, ar-*H*), 3.77 (s, 3H,  $\text{OCH}_3$ ), 3.16-3.05 (m, 1H, *CH*), 2.81 (dd,  $J$  = 15.8, 5.3 Hz, 1H), 2.53 (dd,  $J$  = 15.8, 7.5 Hz, 1H,  $\text{CH}_2$ ), 1.29 (d,  $J$  = 7.0 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 168.1, 159.1, 151.6, 127.4, 120.1, 110.3, 102.1, 55.4, 36.3, 27.9, 19.9.

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 192.1 (49), 178.1 (12), 177.1 (100), 150.1 (22), 149.1 (10), 133.1 (18), 121.1 (24), 91.1 (10), 77.1 (14).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 15 min): 22.98 min.

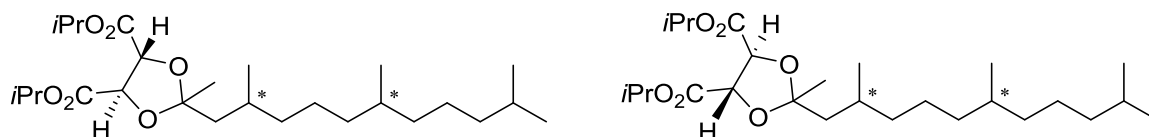
**HPLC**: *Daicel* Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 97:03, 0.5 mL/min;  $T$  = 25 °C, 208 nm,  $t_R$  = 19.9 min and 23.9 min.

Obtained data are in accordance with literature data.<sup>[143]</sup>

## 8.4 Hydrogenation of vitamin E side chain precursors

### 8.4.1 Derivatization for the analysis of the hydrogenation products

#### (-)-D-Diisopropyl-tartrade-acetal (D-4.18) and (+)-L-diisopropyl-tartrade-acetal (L-4.18)



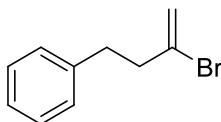
Both acetals were synthesized in accordance to literature-known procedures, by the use of trimethylsilyl triflate.<sup>[88]</sup>

**GC** (CP-Sil 88 (50 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 90 kPa  $\text{H}_2$  (163  $^\circ\text{C}$  – 160 min – 5  $^\circ\text{C}/\text{min}$  – 180  $^\circ\text{C}$  – 10 min): L-acetal  $t_{\text{R}}$  = 148.5 min (3*S*,7*R*), 150.5 min [(3*R*,7*S*) + (3*S*,7*S*)], 154.5 min (3*R*,7*R*); D-acetal:  $t_{\text{R}}$  = 148.5 min (3*R*,7*S*), 150.5 min [(3*S*,7*R*) + (3*R*,7*R*)], 154.5 min (3*S*,7*S*).

## 8.5 Hydrogenation of vinylbromides and chlorides

### 8.5.1 Synthesis of vinyl bromides and chlorides

#### 4-Phenyl-2-bromobut-1-ene (5.8)



4-Phenyl-1-butyne (1.80 g, 1.94 mL, 13.8 mmol, 1.00 eq.) was added dropwise to a 1 M solution of boron tribromide (6.91 mL, 6.91 mmol, 0.50 eq.) in  $\text{CH}_2\text{Cl}_2$  at  $-78\text{ }^\circ\text{C}$ . The solution was allowed to warm to room temperature over a period of 3 h. Glacial acetic acid (19.0 mL) was added to the reaction mixture and stirred for 1 h. The mixture was quenched with water (10 mL), extracted with pentane ( $3 \times 20\text{ mL}$ ) and the combined organic layers were washed with sat.  $\text{NaHCO}_3$  solution ( $\sim 4 \times 15\text{ mL}$ ) until the pH of the water phase stays basic followed by water (15 mL) and brine (15 mL). After drying over  $\text{MgSO}_4$ , the solvent was removed under reduced pressure. The crude product as diluted with pentane (1 mL) and purified over a plug of silica ( $d \times h$ :  $3 \times 4\text{ cm}$ ), followed by elution with pentane (300 mL). The solvent was removed under reduced pressure to obtain the crude vinylbromide as pale yellow liquid. The crude was purified by bulb-to-bulb distillation (20 mbar,  $90\text{ }^\circ\text{C}$ ) to obtain the vinylbromide as pale yellow liquid which was filtered over a plug of silica ( $d \times h$ :  $3 \times 4\text{ cm}$ ), followed by elution with pentane (300 mL). The solvent was removed under reduced pressure to obtain 4-phenyl-2-bromobut-1-ene (1.90 g, 9.00 mmol, 65%) as a colorless liquid in 95% purity. Final purification by semipreparative HPLC (OD-H, hexane,  $8.0\text{ mL/min}$ ,  $25\text{ }^\circ\text{C}$ ) afforded 4-phenyl-2-bromobut-1-ene (75% recovery) as a colorless liquid; purity  $>99.5\%$

$\text{C}_{10}\text{H}_{11}\text{Br}$  (211.10 g/mol):

**TLC:**  $R_f = 0.56$  ( $\text{SiO}_2$ , pentane: $\text{Et}_2\text{O}$  (100:1),  $\text{KMnO}_4$ ).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 7.36\text{--}7.26$  (m, 2H, ar-H),  $7.25\text{--}7.20$  (m, 3H, ar-H),  $5.56\text{--}5.50$  (m, 1H,  $\text{C}=\text{CH}_2$ ),  $5.41$  (d,  $J = 1.7\text{ Hz}$ , 1H,  $\text{C}=\text{CH}_2$ ),  $2.90$  (dd,  $J = 8.8, 6.5\text{ Hz}$ , 2H,  $\text{CH}_2$ ),  $2.77\text{--}2.71$  (m, 2H,  $\text{CH}_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 140.5$  (s, ar- $q\text{C}$ ),  $133.7$  (s,  $\text{C}=\text{CH}_2$ ),  $128.6$  (s, ar-C),  $128.5$  (s, ar-C),  $126.3$  (s, ar-C),  $117.3$  (s,  $\text{C}=\text{CH}_2$ ),  $43.4$  (s,  $\text{CH}_2$ ),  $34.5$  (s,  $\text{CH}_2$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3062 (w), 3027 (w), 2929 (w), 2859 (w), 1628 (m), 1496 (w), 1454 (m), 1185 (m), 1115 (m), 1073 (m), 1030 (m), 886 (m), 838 (w), 748 (m), 698 (s), 628 (s).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 212.0 (1), 210.0 (1), 131.1 (47), 91.1 (100), 65.1 (10).

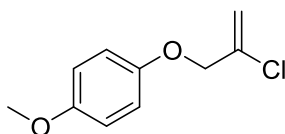
**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 13.52 min.

**HPLC**: *Daicel*, Chiralcel OJ (0.46 cm  $\times$  25 cm, heptane, 0.3 mL/min, 25 °C, 217 nm):  $t_R$  = 28.9 min.

**Semipreparative HPLC**: *Daicel*, Chiralcel OD (2 cm  $\times$  25 cm, heptane, 8.0 mL/min, 208 nm): 16.8 min, 24.8 min (impurity).

Obtained data are in accordance with literature data.<sup>[144]</sup>

### 1-((2-Chloroallyl)oxy)-4-methoxybenzene (5.27)



A 2-necked flask equipped with a reflux condenser and a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold was charged with anhydrous potassium carbonate (4.98 g, 36.0 mmol, 2.00 eq.) and 4-methoxyphenol (2.28 g, 18.0 mmol, 1.00 eq.). The apparatus was flushed for 5 min with argon and acetone (75 mL) followed by 2,3-dichloroprop-1-ene (3.00 g, 2.49 mL, 27.0 mmol, 1.50 eq.) were added. The reaction mixture was stirred for 18 h at reflux and potassium carbonate was filtered off. Evaporation of the solvent and purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 2  $\times$  19 cm, pentane:Et<sub>2</sub>O (50:1)) afforded the product (2.26 g, 11.4 mmol, 63%) as a colorless liquid.

C<sub>10</sub>H<sub>11</sub>ClO<sub>2</sub> (198.65 g/mol):

**TLC**:  $R_f$  = 0.43 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (50:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 6.91–6.81 (m, 4H, ar-*H*), 5.55 (q,  $J$  = 1.6 Hz, 1H, C=CH<sub>2</sub>), 5.43 (q,  $J$  = 1.3 Hz, 1H, C=CH<sub>2</sub>), 4.54 (t,  $J$  = 1.3 Hz, 2H, CH<sub>2</sub>), 3.78 (s, 3H, OCH<sub>3</sub>).

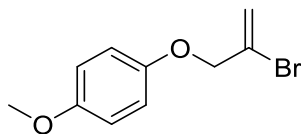
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 154.6 (s, ar-<sub>q</sub>C), 152.1 (s, ar-<sub>q</sub>C), 136.8 (s, C=CH<sub>2</sub>), 116.2 (s, ar-C), 114.8 (s, ar-C), 113.7 (s, C=CH<sub>2</sub>), 71.2 (s, OCH<sub>2</sub>), 55.8 (s, OCH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3001 (w), 2934 (w), 2835 (w), 1639 (w), 1507 (s), 1458 (w), 1389 (w), 1229 (m), 1181 (w), 1108 (w), 1051 (m), 892 (w), 824 (m), 766 (w), 728 (w), 632 (s).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 200.0 (5), 198.0 (15), 123.1 (100), 95.0 (13).

**GC-MS** (Restek Rtx-5MS (30 m × 0.25 mm × 0.25 m) 100 kPa He (50 °C – 2 min – 30 °C/min – 250 °C – 5 min):  $t_R$  = 6.91 min (**5.27**+H<sub>2</sub>-Cl), 7.69 min (**5.27**), 8.18 min (**5.27**+H<sub>2</sub>).

**1-((2-Bromoallyl)oxy)-4-methoxybenzene (**5.26**)**



A 2-necked flask equipped with a reflux condenser and a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold was charged with anhydrous potassium carbonate (4.98 g, 36.0 mmol, 2.00 eq.) and 4-methoxyphenol (2.28 g, 18.0 mmol, 1.00 eq.). The apparatus was flushed for 5 min with argon and acetone (75 mL) followed by 2,3-dichloroprop-1-ene (6.75 g, 3.31 mL, 27.0 mmol, 1.50 eq.) were added. The reaction mixture was stirred for 16 h at reflux and potassium carbonate was filtered off. Evaporation of the solvent and purification by column chromatography (SiO<sub>2</sub>, d × h: 3 × 20 cm, pentane:Et<sub>2</sub>O (90:1)) afforded the product (3.27 g, 13.5 mmol, 75%) as a colorless liquid.

C<sub>10</sub>H<sub>11</sub>BrO<sub>2</sub> (243.10 g/mol):

**TLC**:  $R_f$  = 0.24 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (100:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 6.96-6.73 (m, 4H, ar-H), 5.99 (q,  $J$  = 1.8 Hz, 1H, C=CH<sub>2</sub>), 5.67 (dt,  $J$  = 2.3, 1.3 Hz, 1H, C=CH<sub>2</sub>), 4.60 (t,  $J$  = 1.5 Hz, 2H, CH<sub>2</sub>), 3.77 (s, 3H, OCH<sub>3</sub>).

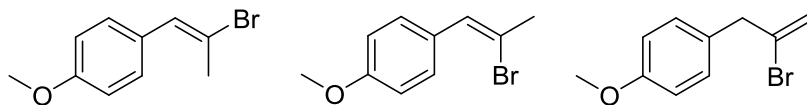
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 154.5 (s, ar-qC), 152.0 (s, ar-qC), 127.7 (s, C=CH<sub>2</sub>), 117.8 (s, C=CH<sub>2</sub>), 116.2, 114.8, 72.7 (OCH<sub>2</sub>), 55.8 (s, OCH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 244.0 (10), 242.0 (11), 124.1 (10), 123.1 (100), 95.1 (15).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 13.55 min.

**GC-MS** (Restek Rtx-5MS (30 m × 0.25 mm × 0.25 m) 100 kPa He (50 °C – 2 min – 30 °C/min – 250 °C – 5 min):  $t_R$  = 6.93 min (**5.26**+H<sub>2</sub>-Br), 8.15 min (**5.26**), 8.62 (**5.26**+H<sub>2</sub>).

Obtained data are in accordance with literature data.<sup>[145]</sup>

**(*E*)-1-(2-Bromoprop-1-en-1-yl)-4-methoxybenzene ((*E*)-5.29), (*Z*)-1-(2-bromoprop-1-en-1-yl)-4-methoxybenzene ((*Z*)-5.30), 1-(2-bromoallyl)-4-methoxybenzene (5.31)**

A solution of triphenyl phosphite (3.00 g, 2.53 mL, 9.38 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was cooled to -60 °C and bromine (1.63 g, 526 μL, 10.2 mmol, 1.20 eq.) was added dropwise. Triethylamine (1.12 g, 1.56 mL, 11.1 mmol, 1.18 eq.) and 4-methoxyphenylacetone (1.40 g, 1.31 mL, 8.53 mmol) were added to the pale orange solution. The reaction mixture was stirred for 18 h, while warming to room temperature, and stirred for further 2 h at reflux. All volatiles were evaporated under reduced pressure. The residue was filtered over a plug of silica (d × h: 3 × 5 cm, pentane:Et<sub>2</sub>O (90:1)) to afford a mixture of *E*, *Z* and terminal vinyl bromide (1.35 g, 5.94 mmol, 63%). The mixture of isomers was purified by semipreparative HPLC (OD-H, hexane, 8.0 mL/min, 25 °C) to afford the pure (*E*)-isomer and the terminal and the (*Z*)-isomer as a mixture.

C<sub>10</sub>H<sub>11</sub>BrO (227.10 g/mol):

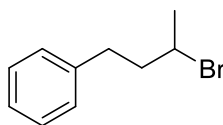
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.53 (d, *J* = 8.8 Hz, 2H, ar-*H*), 6.89 (d, *J* = 8.9 Hz, 2H, ar-*H*), 6.66 (s, 1H, C=CH), 3.82 (s, 3H, OCH<sub>3</sub>), 2.47 (d, *J* = 1.4 Hz, 3H, CH<sub>3</sub>).

<sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>): δ/ppm = 159.0 (s, ar-<sub>q</sub>C), 130.2 (s, ar-C), 128.8 (s, ar-<sub>q</sub>C), 127.5 (s, C=CH), 120.3 (s, C=CH), 113.6 (s, ar-C), 55.4 (s, OCH<sub>3</sub>), 30.8 (s, CH<sub>3</sub>).

**Semipreparative HPLC:** Daicel, Chiralcel OD (2 cm × 25 cm, heptane, 8 mL/min, 220 nm): 28.5 min (*Z*), 32.5 min (terminal), 39.5 min (*E*).

### 8.5.2 Hydrogenation products of vinyl bromides and chlorides

#### (3-Bromobutyl)benzene (**5.9**)



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP7** using iridium catalysts. The racemic sample was prepared according to general procedure **GP7** by the use of racemic catalyst **5.11**.

$\text{C}_{10}\text{H}_{13}\text{Br}$  (213.13 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ): 7.37-7.24 (m, 5H, ar-*H*), 4.11 (m, 1H, *CHBr*), 2.89-2.75 (m, 2H, *CH*<sub>2</sub>Ph), 2.20-2.10 (m, 2H, *CH*<sub>2</sub>CH), 1.75 (d,  $J = 10.5$  Hz, 3H, *CH*<sub>3</sub>).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ): 140.8 (s, ar-*C*), 128.4 (s, ar-*C*), 128.5 (s, ar-*C*), 126.0 (s, ar-*C*), 50.8 (s, *CHBr*), 42.6 (s, *CH*<sub>2</sub>CH), 33.9 (s, *CH*<sub>2</sub>Ph), 26.5 (s, *CH*<sub>3</sub>)

**HPLC**: *Daicel*, Chiralcel OJ (0.46 cm  $\times$  25 cm, heptane, 0.3 mL/min, 25 °C, 217 nm):  $t_R$  = 28.9 min, 33.4 min (overlay with substrate).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 14.56 min, 7.61 min (**5.9-Br**).

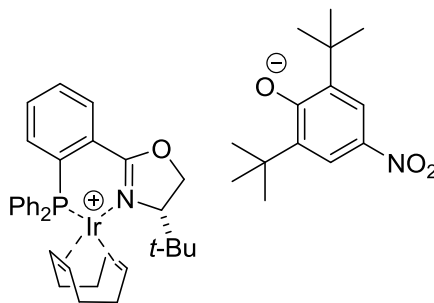
Obtained data are in accordance with literature data.<sup>[146]</sup>



## 8.6 Hydrogenation of $\alpha,\beta$ -unsaturated nitriles

### 8.6.1 Synthesis of catalyst and characterization of intermediates

#### Iridium *tert*-butyl PHOX *para*-nitro phenolate complex (6.106)



A flame dried Schlenk flask was charged with  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (52.0 mg, 77.4  $\mu\text{mol}$ , 0.50 eq.), sodium 2,6-di(*tert*-butyl)-4-nitrophenolate (46.6 mg, 170  $\mu\text{mol}$ , 1.10 eq.), (*S*)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline (60.0 mg, 155  $\mu\text{mol}$ , 1.00 eq.) and  $\text{CH}_2\text{Cl}_2$  (2 mL) was added. The reaction mixture was stirred for 4 h at room temperature. The solution was filtered through a plug of celite ( $d \times h$ : 0.5  $\times$  1 cm), eluted with  $\text{CH}_2\text{Cl}_2$  (5 mL) and all volatiles were evaporated in HV. The residue was washed with  $\text{Et}_2\text{O}$  (3  $\times$  3 mL) to afford the product (121 mg, 129  $\mu\text{mol}$ , 83%) as a red solid.

$\text{C}_{47}\text{H}_{58}\text{BF}_{24}\text{IrN}_2\text{O}_4\text{P}$  (938.18 g/mol):

**MP:** 147-152  $^\circ\text{C}$ .

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.24-8.20 (m, 1H, ar-*H*), 7.95 (s, 2H, ar-*H*), 7.71-7.67 (m, 1H, ar-*H*), 7.63-7.58 (m 1H, ar-*H*), 7.56-7.40 (m, 8H, ar-*H*), 7.29-7.25 (m, 1H, ar-*H*), 7.04 (s, 2H, ar-*H*), 5.11 (s br, 1H, COD), 4.95 (s, br, 1H, COD), 4.58-4.55 (m, 2H, oxazoline), 4.04-3.99 (m, 1H, oxazoline), 3.42-3.39 (m, 1H, oxazoline), 2.95 (s br, 1 H, COD), 2.55-2.37 (m, 4H, COD), 2.04-1.92 (m, 2H, COD), 1.65-1.55 (m, 1H, COD), 1.44-1.35 (s br, 1H, COD), 1.35 (s, 18H, 2  $\times$   $\text{C}(\text{CH}_3)_3$ ), 0.62 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 181.0 (s, ar-*C* counterion), 164.1, 164.1, 139.0 (s, ar-*C* counterion), 134.8, 134.8, 134.4, 134.4, 134.3, 134.2, 134.2, 133.4, 133.3, 132.8, 132.8, 132.6, 132.6, 132.0, 132.0, 130.2, 129.8, 129.7, 129.5, 129.4, 128.9, 128.8, 127.7, 127.2, 126.9, 123.1 (s, ar-*C* counterion), 123.0, 122.4, 98.9, 98.8, 94.0, 93.9, 77.4, 74.5, 70.4, 63.0, 62.2, 37.0, 35.2, 34.5, 32.9, 29.9 (s,  $\text{C}(\text{CH}_3)_3$ ), 28.3, 27.0, 25.8, 25.4.

**$^{31}\text{P}\{^1\text{H}\}$  NMR** (162 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 16.6 (s).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3059 (w), 2948 (w), 2898 (w), 1589 (m), 1533 (w), 1481 (m), 1435 (w), 1369 (m), 1239 (s), 1194 (m), 1135 (m), 1016 (w), 968 (w), 920 (m), 810 (w), 743 (m), 697 (m).

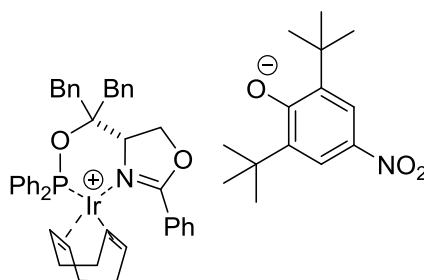
**MS** (ESI (+), 50 V, 200 °C,  $\text{CH}_2\text{Cl}_2$ )  $m/z$  (%): 690.2 (6), 689.2 (36), 688.2 (100), 687.3 (27), 686.1 (60).

**MS** (ESI (-), 50 V, 200 °C,  $\text{CH}_2\text{Cl}_2$ )  $m/z$  (%): 250.1 (16), 248.9 (100).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{33}\text{H}_{38}\text{IrNOP}^+$ : 688.2316 [ $\text{M}-4\text{-NO}_2\text{-2-5-di-tert-butyl-phenolate}]^+$ ; found: 688.2325.

$[\alpha]_D^{20} = -220$  ( $c = 0.18$ ,  $\text{CHCl}_3$ ).

### Iridium SerPHOX *para*-nitro phenolate complex (6.108)



A flame dried Schlenk flask was charged with  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (52.0 mg, 77.4  $\mu\text{mol}$ , 0.50 eq.), sodium 2,6-di(*tert*-butyl)-4-nitrophenolate (46.6 mg, 170  $\mu\text{mol}$ , 1.10 eq.), (*S*)-4-(2-(((diphenylphosphanyl)oxy)-1,3-diphenylpropan-2-yl)-2-phenyl-4,5-dihydrooxazole (83.9 mg, 155  $\mu\text{mol}$ , 1.00 eq.) and  $\text{CH}_2\text{Cl}_2$  (2 mL) was added. The reaction mixture was stirred for 1 h at room temperature. The solution was filtered through a plug of celite ( $d \times h$ : 0.5  $\times$  1 cm), eluted with  $\text{CH}_2\text{Cl}_2$  (5 mL) and all volatiles were evaporated in HV. The residue (150 mg) was dissolved in THF (1.00 mL) and hexane (10.0 mL) was added while stirring. The precipitate was filtered off and this procedure was repeated once to obtain the product (80.0 mg, 73.2  $\mu\text{mol}$ , 47%) as an orange solid.

$\text{C}_{58}\text{H}_{64}\text{IrN}_2\text{O}_5\text{P}$  (1092.35 g/mol):

**MP**: 137 °C, decomposition.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 8.40 (d,  $J = 7.6$  Hz, 2H, ar-*H*), 8.21-8.14 (m, 2H, ar-*H*), 7.92-7.84 (m, 4H, ar-*H*), 7.72-7.68 (m, 4H, ar-*H*), 7.53-7.37 (m, 6H, ar-*H*), 7.19-7.06 (m, 7H, ar-*H*), 6.77 (d,  $J = 7.3$  Hz, 2H, ar-*H*), 5.11-5.05 (s br, 1H, COD), 5.03-4.97 (m, 2H,  $\text{CH}_2\text{O}$ ), 4.77-4.71 (m, 1H, CHN), 3.80-3.66 (m, 2H, COD), 3.05-2.88 (m, 3H,  $\text{CH}_2\text{Ph}$ ), 2.70

(d,  $J = 14.9$  Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 2.55-2.45 (m, 1H, COD), 2.42-2.34 (m, 1H, COD), 2.28-2.12 (m, 3H, COD), 1.72-1.59 (m, 2H, COD), 1.55-1.48 (m, 1H, COD), 1.33 (s, 19H,  $\text{C}(\text{CH}_3)_3$  and COD).

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = decomposition low sensitivity.

$^{31}\text{P}\{^1\text{H}\}$  NMR (162 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 99.5 (s).

IR (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2948 (w), 2913 (w), 1594 (w), 1481 (w), 1371 (w), 1382 (w), 1345 (m), 1243 (s), 1197 (m), 1136 (m), 1102 (m), 1017 (m), 913 (m), 809 (w), 743 (m), 701 (m), 618 (w).

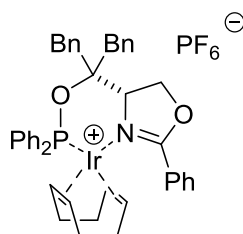
MS (ESI (+), 50 V, 200 °C,  $\text{CH}_2\text{Cl}_2$ )  $m/z$  (%): 844.5 (13), 843.5 (55), 842.6 (100), 841.7 (97), 840.4 (71), 839.6 (32).

MS (ESI (-), 50 V, 200 °C,  $\text{CH}_2\text{Cl}_2$ )  $m/z$  (%): 250.1 (16), 248.9 (100).

HRMS (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{44}\text{H}_{44}\text{IrNO}_2\text{P}^+$ : 842.2735 [ $\text{M}-4\text{-NO}_2\text{-2-5-di-tert-butyl-phenolate}]^+$ ; found: 842.2736.

$[\alpha]_D^{20} = -17$  ( $c = 0.09$ ,  $\text{CHCl}_3$ ).

### (S)-SerPHOX $\text{PF}_6$ iridium complex



A flame dried Schlenk flask was charged with  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (48.5 mg, 72.3  $\mu\text{mol}$ , 0.50 eq.), sodium  $\text{AgPF}_6$  (40.0 mg, 72.3  $\mu\text{mol}$ , 1.10 eq.), (S)-4-(2-((diphenylphosphanyl)oxy)-1,3-diphenylpropan-2-yl)-2-phenyl-4,5-dihydrooxazole (78.3 mg, 144  $\mu\text{mol}$ , 1.00 eq.) and  $\text{CH}_2\text{Cl}_2$  (2 mL) was added. The reaction mixture was stirred for 4 h at room temperature. The solution was filtered through a plug of celite ( $d \times h$ :  $0.5 \times 1$  cm), eluted with  $\text{CH}_2\text{Cl}_2$  (5 mL) and all volatiles were evaporated in HV. The residue was washed with  $\text{Et}_2\text{O}$  ( $3 \times 3$  mL) to afford the product (121 mg, 129  $\mu\text{mol}$ , 83%) as a red solid.

$\text{C}_{44}\text{H}_{44}\text{F}_6\text{IrNO}_2\text{P}_2$  (987.00 g/mol):

MP: 155-160 °C.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 8.41 (d,  $J$  = 7.7 Hz, 1H, ar-*H*), 8.25-8.09 (m, 1H, ar-*H*), 7.95-6.84 (m, 20H, ar-*H*), 6.85-6.70 (m, 1H, ar-*H*), 5.19-5.07 (m, 1H), 5.06-4.96 (m, 1H), 4.81-4.67 (m, 1H), 3.87-3.70 (m, 1H), 3.08-2.84 (m, 3H), 2.72 (d,  $J$  = 14.8 Hz, 1H), 2.61-2.09 (m, 5H), 1.72-1.63 (m, 2H), 1.60-1.50 (m, 2H), 1.48-1.32 (m, 2H).

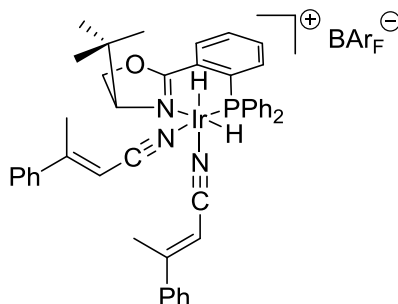
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 174.4 (s, C=N), 136.5, 136.1, 136.0, 135.2 (d,  $J$  = 15.5 Hz), 134.5, 134.3, 134.0 (d,  $J$  = 2.1 Hz), 132.2 (d,  $J$  = 11.7 Hz), 132.2 (d,  $J$  = 2.3 Hz), 131.9, 131.0, 130.1 (d,  $J$  = 11.2 Hz), 129.8, 129.4, 128.8 (d,  $J$  = 11.1 Hz), 128.8, 128.3, 127.9, 124.4, 104.5 (d,  $J$  = 11.4 Hz), 104.5 (d,  $J$  = 11.4 Hz), 96.5 (d,  $J$  = 13.7 Hz), 89.5 (d,  $J$  = 7.2 Hz), 72.2 (d,  $J$  = 5.1 Hz), 70.8, 69.0, 65.6, 44.3 (d,  $J$  = 5.9 Hz), 41.5 (d,  $J$  = 1.6 Hz), 36.6 (d,  $J$  = 3.6 Hz), 32.3 (d,  $J$  = 1.8 Hz), 29.2 (d,  $J$  = 1.6 Hz), 26.2.

**$^{31}\text{P}\{^1\text{H}\}$  NMR** (162 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 99.4 (s), -144.4 (sept,  $J$  = 711 Hz).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3061 (w), 2925 (w), 2028 (w), 1597 (w), 1495 (w), 1437 (w), 1253 (w), 1101 (w), 831 (s), 740 (m), 696 (s), 555 (s).

$[\alpha]_D^{20}$  = -38 ( $c$  = 0.29,  $\text{CHCl}_3$ ).

### Iridium(III)–dihydride-species (6.13)



To a solution of (*E*)-3-phenylbut-2-enenitrile (18.4 mg, 129  $\mu\text{mol}$ , 4.00 eq) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL), diphenylphosphine-*tert*-butyl-iridium-PHOX (50.0 mg, 32  $\mu\text{mol}$ , 1.00 eq) was added. The reaction vial was equipped with a magnetic stir bar and placed in an autoclave that was pressurized to 70 bar with  $\text{H}_2$ . The reaction mixture was stirred at 800 rpm for 2 h. After this time hydrogen was released and the solvent removed under reduced pressure in HV (0.05 mbar). The obtained yellow oil was washed with pentane ( $5 \times 2$  mL) and the residue dried in HV to afford a colorless foam (41.2 mg, 23.8  $\mu\text{mol}$ , 71%).

**MP:** 55°C, decomposition.

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.35 (dd,  $J$  = 7.9 Hz, 3.8 Hz, 1H, ar-*H*), 7.77 (s, 8H,  $\text{BAr}_\text{F}$ ), 7.66 – 7.37 (m, 28H, ar-*H* and  $\text{BAr}_\text{F}$ ), 6.95 – 6.90 (m, 1H, ar-*H*), 6.02 (s, 1H, C=CH),

5.58 (br s, 1H, C=CH), 4.68 (dd,  $J = 9.4$  Hz, 3.7 Hz, 1H, OCH<sub>2</sub>), 4.49 (t,  $J = 9.4$  Hz, 1H, NCH), 4.26 (dd,  $J = 9.5$  Hz, 3.6 Hz, 1H, OCH<sub>2</sub>), 2.61 (s, 3H, CH<sub>3</sub>), 1.99 (br s, 3H, CH<sub>3</sub>), 0.78 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), -20.37 – -20.58 (m, 2H, 2 × Ir-H).

<sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ /ppm = 165.8 (d,  $J_{CP} = 2$  Hz), 165.6, 162.3 (q,  $J_{BC} = 50$  Hz, BAr<sub>F</sub>), 137.6, 135.4 (BAr<sub>F</sub>), 134.8 (d,  $J_{CP} = 12.0$  Hz), 133.8, 132.6 (d,  $J_{CP} = 11.3$  Hz), 133.3 (d,  $J_{CP} = 7$  Hz), 133.2 (d,  $J_{CP} = 9$  Hz), 133.0 (d,  $J_{CP} = 2$  Hz), 132.2 (d,  $J_{CP} = 9$  Hz), 132.1, 132.1, 131.8 (d,  $J_{CP} = 2$  Hz), 129.6, (129.5 (qq,  $J_{CF} = 30$  Hz,  $J_{BC} = 3$  Hz, BAr<sub>F</sub>), 129.4, 129.4, 129.3, 129.2, 129.1 (d,  $J_{CP} = 6$  Hz), 126.4, 126.1, 125.2 (q,  $J_{CF} = 272$  Hz, BAr<sub>F</sub>), 118.0 (sept,  $J_{CF} = 4$  Hz, BAr<sub>F</sub>), 93.8, 93.8, 76.9, 70.4, 35.8, 26.5, 21.3, 20.6. Quaternary carbons with <sup>1</sup> $J_{CP}$  coupling were not detected.

<sup>31</sup>P{<sup>1</sup>H} NMR (161 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ /ppm = 8.23.

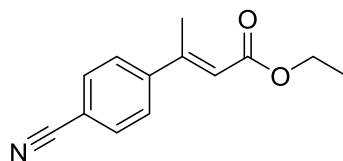
IR (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3063 (w), 2966 (w), 1609 (m), 1576 (w), 1438 (m), 1353 (s), 1314 (w), 1273 (s), 1242 (w), 1115 (s), 1020 (w), 1001 (w), 966 (w), 886 (m), 839 (m), 778 (w), 754 (m), 712 (m), 692 (m), 681 (m), 670 (m).

MS (ESI, 70 eV, 50 °C)  $m/z$  (%): 868.3 (11), 726.2 (37), 725.3 (100), 724.4 (31), 726.2 (57).<sup>[I]</sup>

HRMS (ESI, 180 °C, 4500 V): ( $m/z$ ) calc. for C<sub>25</sub>H<sub>28</sub>IrNOP: 582.1538 [M-2×(E)-3-phenylbut-2-enenitrile]<sup>+</sup>; found: 582.1533.

$[\alpha]_D^{20} = +43.3$  (c = 0.38, CHCl<sub>3</sub>).

[I] = Ms was determined out of the reaction mixture before purification. This allowed detection of the mass of complex 4-BAr<sub>F</sub>. Determination of the mass of the isolated material gave predominantly [M-2×(E)-3-phenylbut-2-enenitrile]<sup>+</sup>; and [M-(E)-3-phenylbut-2-enenitrile]<sup>+</sup>.

**Ethyl (*E*)-3-(4-cyanophenyl)but-2-enoate (6.11)**

To a suspension of sodium hydride (60% in mineral oil, 484 mg, 12.1 mmol, 1.00 eq.) in THF (40 mL) was added ethyl diethylphosphonoacetate (2.71 g, 2.40 mL, 12.1 mmol, 1.00 eq.) dropwise at 0 °C and the mixture was stirred till gas evolution had ceased. 4-Acetylbenzonitrile (1.75 g, 12.1 mmol, 1.00 eq.) was added in small portions and the solution was stirred for 16 h at room temperature. H<sub>2</sub>O (40 mL) was added followed by extraction with ethyl acetate (3 × 30 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the solvent was evaporated under reduced pressure. Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 30 cm, cyclohexane:ethyl acetate (13:1)) afforded the product (900 mg, 4.18 mmol, 35%) as a colorless solid and 1.05 g of a mixture of the (*E/Z*)-isomers.

C<sub>13</sub>H<sub>13</sub>NO<sub>2</sub> (215.25 g/mol):

**MP:** 49-50 °C.

**TLC:** R<sub>f</sub> = 0.30 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (15:1)).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.66 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H, ar-*H*), 7.55 (d, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz, 2H, ar-*H*), 6.14 (q, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 1H, C=CH), 4.22 (q, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 2H, OCH<sub>2</sub>), 2.55 (d, <sup>4</sup>J<sub>HH</sub> = 1.3 Hz, 3H, CH<sub>3</sub>), 1.31 (t, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 166.3 (s, C=O), 153.1 (s, C=CH), 146.8 (s, ar-<sub>q</sub>C), 132.4 (s, ar-C), 127.1 (s, ar-C), 119.8 (s, C=CH), 118.6 (s, C≡N), 112.6 (ar-<sub>q</sub>C), 60.3 (s, OCH<sub>2</sub>), 17.9 (s, CH<sub>3</sub>), 14.4 (s, CH<sub>3</sub>).

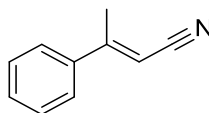
**MS** (EI, 70 eV, 200 °C) *m/z* (%): 216.1 (10), 215.1 (67), 187.1 (30), 186.1 (72), 171.1 (14), 170.1 (100), 169.1 (35), 143.1 (14), 142.1 (34), 141.1 (23), 140.1 (34), 116.1 (28), 115.1 (50).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 25.14 min.

### 8.6.2 Synthesis of $\alpha,\beta$ -unsaturated nitriles and precursors

#### General procedure: Horner–Wadsworth–Emmons reaction GP9

##### (*E*)-3-Phenylbut-2-enenitrile (6.3)



To a stirred suspension of NaH (1.85 g, 46.4 mmol, 1.50 eq., 60% in mineral oil) in THF (100 mL), diethyl cyanomethylphosphonate (6.57 g, 6.00 mL, 37.1 mmol, 1.20 eq.) was added dropwise at 0 °C. The solution was stirred at room temperature until gas evolution had ceased. Acetophenone (3.71 g, 3.61 mL, 30.9 mmol, 1.00 eq.) was added dropwise and the reaction mixture was stirred for 14 h at room temperature. H<sub>2</sub>O (60 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were dried over MgSO<sub>4</sub>. Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 33 cm, pentane:Et<sub>2</sub>O (50:1)) afforded the product (3.79 g, 26.5 mmol, 86%) as a colorless liquid.

C<sub>10</sub>H<sub>9</sub>N (143.19 g/mol):

**TLC:** R<sub>f</sub> = 0.26 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (50:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.52–7.44 (m, 2H, ar-*H*), 7.44–7.37 (m, 3H, ar-*H*), 5.62 (q, <sup>4</sup>J<sub>HH</sub> = 1.1 Hz, 1H, C=CH), 2.47 (d, <sup>4</sup>J<sub>HH</sub> = 1.1 Hz, 3H, CH<sub>3</sub>).

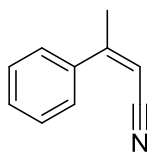
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 159.6 (s, C=CH), 138.0 (s, ar-<sub>q</sub>C), 130.2 (s, ar-C), 128.7 (s, ar-C), 125.8 (s, ar-C), 117.5 (s, C≡N), 95.4 (s, C=CH), 20.0 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 144.1 (12), 143.2 (100), 142.2 (12), 116.1 (34), 115.1 (35), 103.1 (14), 78.1 (21), 77.1 (13).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 15.42 min.

**HPLC:** Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 208 nm): t<sub>R</sub> = 25.2 min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

**(Z)-3-Phenylbut-2-enenitrile (6.43)**

(Z)-3-phenylbut-2-enenitrile (252 mg, 1.76 mmol, 6%) was obtained as minor product in the Horner–Wadsworth–Emmons reaction of cyanomethylphosphonate with acetophenone as a colorless liquid.

C<sub>10</sub>H<sub>9</sub>N (143.19 g/mol):

**TLC:** R<sub>f</sub> = 0.20 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (40:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.59–7.49 (m, 2H, ar-*H*), 7.47–7.39 (m, 3H, ar-*H*), 5.40 (q, <sup>4</sup>J<sub>HH</sub> = 1.5 Hz, 1H, C=CH), 2.28 (d, <sup>4</sup>J<sub>HH</sub> = 1.5 Hz, 3H, CH<sub>3</sub>).

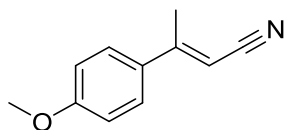
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 161.1 (s, C=CH), 138.0 (s, ar-*qC*), 129.9 (s, ar-*C*), 128.7 (s, ar-*C*), 127.1 (s, ar-*C*), 117.6 (s, C≡N), 95.5 (s, C=CH), 24.7 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 144.1 (11), 143.1 (100), 142.1 (12), 116.1 (29), 115.1 (33), 103.1 (13), 78.1 (18), 77.1 (11).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 16.6 min.

**HPLC:** Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 208 nm): t<sub>R</sub> = 19.5 min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

**(E)-3-(4-Methoxyphenyl)but-2-enenitrile (6.48)**

The α,β-unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (50 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.29 g, 18.5 mmol, 1.20 eq.) and 4'-methoxyacetophenone (2.32 g, 15.5 mmol, 1.00 eq.). H<sub>2</sub>O (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the residue filtered over a plug of silica (d × h: 2 × 10 cm, pentane:Et<sub>2</sub>O (1:1)) to



obtain the product as a (*E/Z*)-mixture (2.40 g). The residue was dissolved in a mixture of pentane:Et<sub>2</sub>O ((2:3), 50 mL) and stored for 12 h at –25 °C. The resulting crystals were filtered off and washed with pentane (3 × 5 mL) to afford the pure (*E*)-isomer (1.56 g, 9.01 mmol, 58%) as colorless crystals.

C<sub>11</sub>H<sub>11</sub>NO (173.21 g/mol):

**MP:** 61–62 °C.

**TLC:** R<sub>f</sub> = 0.15 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.43 (d, <sup>3</sup>J<sub>HH</sub> = 8.9 Hz, 2H, ar-*H*), 6.91 (d, <sup>3</sup>J<sub>HH</sub> = 8.9 Hz, 2H, ar-*H*), 5.54 (s, 1H, C=CH), 3.84 (s, 3H, OCH<sub>3</sub>), 2.43 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 161.5 (s, ar-*qC*), 158.9 (s, C=CH), 130.5 (ar-*qC*), 127.5 (s, ar-*C*), 118.3 (s, C≡N), 114.3 (s, ar-*C*), 93.3 (s, C=CH), 55.6 (s, OCH<sub>3</sub>), 20.1 (s, CH<sub>3</sub>).

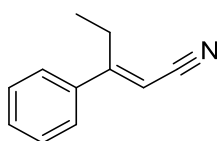
**MS** (EI, 70 eV, 200 °C) *m/z* (%): 174.1 (10), 173.1 (100), 172.1 (13), 158.1 (34), 143.1 (16), 130.1 (18), 103.1 (31), 77.1 (18).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 20.56 min.

**HPLC:** *Daicel*, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 208 nm): t<sub>R</sub> = 19.4 min.

Obtained data are in accordance with literature data.<sup>[147]</sup>

### (*E*)-3-Phenylpent-2-enenitrile (6.54)



The α,β-unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (40 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.29 g, 18.5 mmol, 1.20 eq.) and propiophenone (2.07 g, 15.5 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 25 cm, pentane:Et<sub>2</sub>O (25:1)) afforded the product (1.95 g, 12.3 mmol, 80%) as a colorless liquid.

C<sub>11</sub>H<sub>11</sub>N (157.22 g/mol):

**TLC:** R<sub>f</sub> = 0.54 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.43-7.37 (m, 5H, ar-*H*), 5.49 (s, 1H, C=CH), 2.90 (q,  $^3J_{\text{HH}}$  = 7.6 Hz, 2H,  $\text{CH}_2$ ), 1.13 (t,  $^3J_{\text{HH}}$  = 7.6 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 166.6 (s, ar- $_{\text{q}}\text{C}$ ), 137.5 (s, C=CH), 130.2 (s, ar-C), 129.1 (s, ar-C), 126.5 (s, ar-C), 117.5 (s,  $\text{C}\equiv\text{N}$ ), 95.2 (s, C=CH), 27.4 (s,  $\text{CH}_2$ ), 13.5 (s,  $\text{CH}_3$ ).

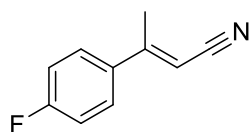
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 158.1 (13), 157.1 (100), 156.2 (71), 142.1 (64), 140.1 (10), 130.1 (18), 129.1 (32), 128.1 (16), 117.1 (14), 116.1 (17), 115.1 (67), 102.1 (10), 91.1 (11), 78.1 (15), 77.1 (16).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_{\text{R}}$  = 17.17 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 215 nm):  $t_{\text{R}}$  = 14.8 min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

### (*E*)-3-(4-Fluorophenyl)but-2-enenitrile (6.57)



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (584 mg, 14.6 mmol, 1.50 eq., 60% in mineral oil) in THF (40 mL), diethyl cyanomethylphosphonate (1.89 mL, 2.07 g, 11.7 mmol, 1.20 eq.) and 4'-fluoroacetophenone (1.34 g, 1.18 mL 9.73 mmol, 1.00 eq.). Purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 5  $\times$  20 cm, pentane: $\text{Et}_2\text{O}$  (40:1)) afforded the product (900 mg, 5.89 mmol, 61%) as a colorless solid.

$\text{C}_{10}\text{H}_8\text{FN}$  (161.18 g/mol):

**MP**: 48-50 °C.

**TLC**:  $R_f$  = 0.28 ( $\text{SiO}_2$ , pentane: $\text{Et}_2\text{O}$  (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.53-7.38 (m, 2H, ar-*H*), 7.17-6.98 (m, 2H, ar-*H*), 5.64-5.46 (m, 1H, C=CH), 2.45 (d,  $J$  = 0.9 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 164.1 (d,  $^1J_{\text{CF}}$  = 251 Hz, ar- $_{\text{q}}\text{C}$ ), 158.6 (s, C=CH), 134.5 (d,  $^4J_{\text{CF}}$  = 3 Hz, ar- $_{\text{q}}\text{C}$ ), 128.0 (d,  $^3J_{\text{CF}}$  = 9 Hz, ar-C), 117.6 (s,  $\text{C}\equiv\text{N}$ ), 116.0 (d,  $^2J_{\text{CF}}$  = 22 Hz, ar-C), 95.6 (d,  $^6J_{\text{CF}}$  = 2 Hz, C=CH), 20.4 (s,  $\text{CH}_3$ ).

**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = -110.1$ .

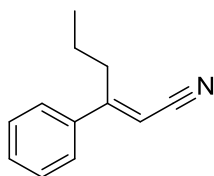
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 3068$  (w), 2928 (w), 2210 (s), 1927 (w), 1904 (w), 1877 (w), 1656 (w), 1598 (s), 1512 (s), 1444 (s), 1412 (m), 1224 (s), 1212 (m), 1112 (m), 941 (w), 829 (s), 795 (s), 746 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 162.1 (11), 161.1 (100), 160.1 (10), 146.1 (16), 134.1 (37), 133.1 (42), 126.1 (13), 121.1 (13), 101.1 (11), 96.1 (31), 75.0 (10).

**EA** ( $\text{C}_{10}\text{H}_8\text{FN}$ ): calc.: C 74.52, H 5.00, N 8.69; found: C 74.52, H 5.07, N 8.88.

**GC** (*Chiraldex*  $\gamma$ -cyclodextrin TFA G-TA (30 m  $\times$  0.25 mm  $\times$  0.12  $\mu\text{m}$ ), 60 kPa  $\text{H}_2$  (50 °C – 0 min – 10 °C/min – 100 °C – 0 min – 2 °C/min – 140 °C – 10 °C/min – 160 °C – 5 min):  $t_{\text{R}} = 22.49$  min.

### (*E*)-3-Phenylhex-2-enenitrile (6.55)



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (584 mg, 14.6 mmol, 1.50 eq., 60% in mineral oil) in THF (40 mL), diethyl cyanomethylphosphonate (1.89 mL, 2.07 g, 11.7 mmol, 1.20 eq.) and butyrophenone (1.44 g, 1.41 mL 9.73 mmol, 1.00 eq.). Purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 5  $\times$  20 cm, pentane: $\text{Et}_2\text{O}$  (20:1)) afforded the product (1.15 g, 6.72 mmol, 69%) as a colorless liquid.

$\text{C}_{12}\text{H}_{13}\text{N}$  (143.19 g/mol):

**TLC**:  $R_f = 0.48$  ( $\text{SiO}_2$ , pentane: $\text{Et}_2\text{O}$  (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 7.44$ – $7.38$  (m, 5H, ar-*H*), 5.51 (s, 1H,  $\text{C}=\text{CH}$ ), 2.89–2.86 (m, 2H,  $\text{CH}_2$ ), 1.59–1.43 (m, 2H,  $\text{CH}_2$ ), 0.95 (t,  $J = 7.4$  Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 165.1$  (s, ar- $q\text{C}$ ), 137.8 (s,  $\text{C}=\text{CH}$ ), 130.2 (s, ar- $\text{C}$ ), 129.3 (s, ar- $\text{C}$ ), 126.5 (s, ar- $\text{C}$ ), 117.6 (s,  $\text{C}\equiv\text{N}$ ), 96.0 (s,  $\text{C}=\text{CH}$ ), 35.9 (s,  $\text{CH}_2$ ), 21.9 (s,  $\text{CH}_2$ ), 13.7 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 3061$  (w), 2963 (m), 2873 (w), 2214 (s), 1603 (m), 1574 (m), 1495 (w), 1458 (m), 1381 (w), 1336 (w), 1256 (w), 1081 (w), 830 (w), 758 (s), 696 (s), 632 (s).

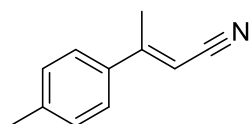
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 171.1 (45), 156.1 (13), 144.1 (20), 143.1 (100), 142.1 (32), 131.1 (12), 129.1 (48), 128.1 (14), 116.1 (16), 115.1 (47), 103.1 (24), 102.1 (13), 78.1 (13), 77.1 (13),

**EA** (C<sub>12</sub>H<sub>13</sub>N): calc.: C 84.17, H 7.65, N 8.18; found: C 83.79, H 7.50, N 8.46.

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 18.59 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min, 25 °C, 208 nm):  $t_R$  = 17.0 min.

**(E)-3-(p-Tolyl)but-2-enenitrile (6.46)**



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.28 mL, 3.00 g, 18.5 mmol, 1.20 eq.) and 4'-methylacetophenone (2.07 mL, 2.08 g, 15.5 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 25 cm, pentane:Et<sub>2</sub>O (30:1)) afforded the product (1.83 g, 11.6 mmol, 75%) as a colorless solid.

C<sub>11</sub>H<sub>11</sub>N (157.22 g/mol):

**MP**: 36-37 °C.

**TLC**:  $R_f$  = 0.41 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.37 (d,  $^3J_{HH}$  = 8.2 Hz, 2H, ar-*H*), 7.21 (d,  $^3J_{HH}$  = 8.2 Hz, 2H, ar-*H*), 5.60 (q,  $^4J_{HH}$  = 1.0 Hz, 1H, C=CH), 2.45 (d,  $^4J_{HH}$  = 1.0 Hz, 3H, CH<sub>3</sub>), 2.38 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 159.7 (s, C=CH), 140.9 (s, ar-*qC*), 135.5 (s, ar-*qC*), 129.7 (s, ar-*C*), 126.0 (s, ar-*C*), 118.1 (s, C≡N), 94.7 (s, C=CH), 21.5 (s, CH<sub>3</sub>), 20.3 (s, CH<sub>3</sub>).

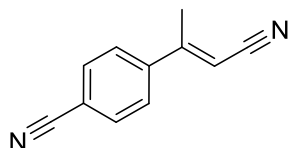
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 58.1 (11), 157.1 (100), 156.1 (54), 142.1 (34), 140.1 (11), 130.1 (15), 129.1 (26), 128.1 (11), 116.1 (10), 115.1 (34), 91.1 (20), 65.1 (10).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 18.62 min.

**HPLC:** *Daicel*, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 208 nm):  $t_R$  = 15.5 min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

**(E)-4-(1-Cyanoprop-1-en-2-yl)benzonitrile (6.61)**



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (926 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.28 g, 18.5 mmol, 1.20 eq.) and 4-acetylbenzonitrile (2.24 g, 15.4 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 25 cm, pentane:Et<sub>2</sub>O (3:1)) afforded the product (180 mg, 1.07 mmol, 7%) as a colorless solid.

C<sub>11</sub>H<sub>8</sub>N<sub>2</sub> (168.20 g/mol):

**MP:** 134-136 °C.

**TLC:**  $R_f$  = 0.47 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (1:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.70 (d,  $^3J_{HH}$  = 8.6, 2H, ar-*H*), 7.56 (d,  $^3J_{HH}$  = 8.5 Hz, 2H, ar-*H*), 5.68 (q,  $^4J_{HH}$  = 1.0 Hz, 1H, C=CH), 2.48 (d,  $^4J_{HH}$  = 1.1 Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 157.9 (s, ar-*qC*), 142.6 (s, C=CH), 132.8 (s, ar-*C*), 126.8 (s, ar-*C*), 118.2 (s, C≡N), 116.8 (s, C≡N), 114.0 (s, ar-*qC*), 98.8 (s, C=CH), 20.3 (s, CH<sub>3</sub>).

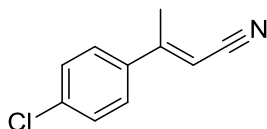
**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3070 (w), 2931 (w), 2214 (s), 1929 (w), 1674 (w), 1609 (m), 1504 (w), 1411 (m), 1336 (m), 1261 (w), 1183 (w), 1134 (w), 1080 (w), 1014 (w), 968 (w), 922 (w), 815 (s), 721 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 169.1 (13), 168.1 (100), 167.1 (12), 141.1 (37), 140.1 (33), 128.1 (26), 114.1 (15), 103.1 (16).

**EA** (C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>): calc.: C 78.55, H 4.79, N 16.66; found: C 78.66, H 5.06, N 16.45.

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 25.53 min.

**HPLC:** *Daicel*, Chiralpak AS-H (0.46 cm × 25 cm, heptane/iso-propanol = 60:40, 0.5 mL/min, 25 °C, 208 nm):  $t_R$  = 24.7 min.

**(E)-3-(4-Chlorophenyl)but-2-enitrile (6.50)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 24.7 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.29 g, 18.5 mmol, 1.20 eq.) and 4'-chloroacetophenone (2.01 mL, 2.49 g, 15.5 mmol, 1.00 eq.). Purification by column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 25$  cm, pentane:Et<sub>2</sub>O (30:1)) afforded the product (2.20 g, 12.4 mmol, 80%) as a colorless solid.

$\text{C}_{10}\text{H}_8\text{ClN}$  (177.63 g/mol):

**MP:** 54-55 °C.

**TLC:**  $R_f = 0.39$  ( $\text{SiO}_2$ , pentane:Et<sub>2</sub>O (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 7.43\text{--}7.34$  (m, 4H, ar-*H*), 5.60 (q,  $^4J_{\text{HH}} = 1.2$  Hz, 1H, C=CH), 2.45 (d,  $^4J_{\text{HH}} = 1.2$  Hz, 3H,  $\text{CH}_3$ ).

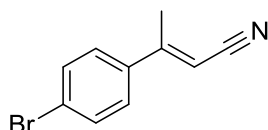
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 158.5$  (s, C=CH), 136.7 (s, ar- $_{\text{q}}\text{C}$ ), 136.5 (s, ar- $_{\text{q}}\text{C}$ ), 129.2 (s, ar-C), 127.3 (s, ar-C), 117.4 (s,  $\text{C}\equiv\text{N}$ ), 96.2 (s, C=CH), 20.3 (s,  $\text{CH}_3$ ).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 179.0 (32), 177.0 (100), 142.1 (51), 137.1 (11), 127.1 (14), 116.1 (12), 115.1 (73), 142.1 (51), 140.1 (15), 137.1 (11), 127.1 (14), 116.1 (12), 115.1 (73), 114.1 (14), 112.0 (23), 75.0 (15).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_{\text{R}} = 20.73$  min.

**HPLC:** Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 220 nm):  $t_{\text{R}} = 19.2$  min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

**(E)-3-(4-Bromophenyl)but-2-enenitrile (6.58)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (926 mg, 23.1 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.29 g, 18.5 mmol, 1.20 eq.) and 4'-bromoacetophenone (3.07 g, 15.4 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 18 cm, pentane:Et<sub>2</sub>O (20:1)) afforded the product (1.08 g, 4.86 mmol, 32%) as a colorless solid.

C<sub>10</sub>H<sub>8</sub>BrN (222.08 g/mol):

**MP:** 54-55 °C.

**TLC:** R<sub>f</sub> = 0.29 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.53 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H, ar-*H*), 7.33 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H, ar-*H*), 5.61 (d, <sup>4</sup>J<sub>HH</sub> = 0.4 Hz, 1H, C=CH), 2.45 (d, <sup>4</sup>J<sub>HH</sub> = 0.4 Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 158.6 (s, C=CH), 137.3 (s, ar-<sub>q</sub>C), 132.2 (s, ar-C), 127.6 (s, ar-C), 124.9 (s, ar-<sub>q</sub>C), 117.5 (s, C≡N), 96.3 (s, C=CH), 20.3 (s, CH<sub>3</sub>).

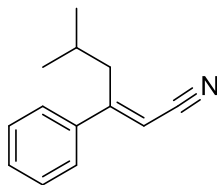
**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3058 (w), 2994 (w), 2964 (w), 2111 (m), 1914 (w), 1602 (m), 1484 (m), 1436 (m), 1400 (m), 1326 (m), 1257 (w), 1083 (m), 1007 (m), 922 (w), 803 (s), 671 (w).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 223.0 (74), 221.0 (75), 142.1 (53), 140.1 (18), 127.1 (22), 116.1 (21), 115.1 (100), 102.1 (15), 77.1 (10), 75.1 (11), 70.6 (10), 50.0 (10).

**EA** (C<sub>10</sub>H<sub>8</sub>BrN): calc.: C 54.08, H 3.63, N 6.31; found: C 54.30, H 3.68, N 6.40.

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 22.71 min.

**HPLC:** Daicel, Chiralpak AS-H (0.46 cm × 25 cm, heptane/iso-propanol = 97:03, 0.5 mL/min, 25 °C, 220 nm): t<sub>R</sub> = 36.5 min.

**(E)-5-Methyl-3-phenylhex-2-enenitrile (6.56)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (584 mg, 14.6 mmol, 1.50 eq., 60% in mineral oil) in THF (40 mL), diethyl cyanomethylphosphonate (1.89 mL, 2.07 g, 11.7 mmol, 1.20 eq.) and 3-methyl-1-phenylbutan-1-one (1.66 mL, 1.58 g, 9.74 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 5  $\times$  25 cm, pentane:Et<sub>2</sub>O (80:1)) afforded the product (720 mg, 3.89 mmol, 40%) as a colorless liquid.

C<sub>13</sub>H<sub>15</sub>N (185.27 g/mol):

**TLC:** R<sub>f</sub> = 0.56 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (80:1)).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.43-7.36 (m, 5H, ar-*H*), 5.52 (s, 1H, C=CH), 2.78 (d, <sup>3</sup>J<sub>HH</sub> = 7.3 Hz, 2H, CH<sub>2</sub>), 1.79-1.65 (m, 1H, CH), 0.93 (d, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 164.5 (s, C=CH), 138.1 (s, ar-*q*C), 130.1 (s, ar-C), 129.0 (s, ar-C), 126.5 (s, ar-C), 117.7 (s, C $\equiv$ N), 96.7 (C=CH), 42.9 (s, CH<sub>2</sub>), 27.7 (s, CH), 22.3 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3062 (w), 2958 (m), 2870 (w), 2214 (s), 1604 (m), 1573 (w), 1494 (w), 1465 (m), 1387 (w), 1369 (w), 1219 (w), 1167 (w), 1080 (w), 927 (w), 828 (m), 801 (m), 774 (m), 756 (s), 695 (s).

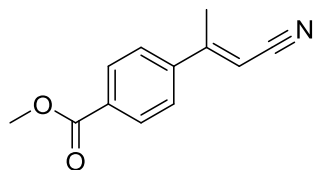
**MS** (EI, 70 eV, 200 °C) *m/z* (%): 185.1 (16), 143.1 (100), 143.1 (100), 115.1 (11).

**HRMS** (EI): (*m/z*) calc. for C<sub>13</sub>H<sub>15</sub>N<sup>+</sup>: 185.1199 [M]<sup>+</sup>; found: 185.1199.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 19.25 min.

**HPLC:** Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 212 nm): t<sub>R</sub> = 13.9 min.



**(E)-Methyl 4-(1-cyanoprop-1-en-2-yl)benzoate (6.60)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (600 mg, 15.0 mmol, 1.50 eq., 60% in mineral oil) in THF (40 mL), diethyl cyanomethylphosphonate (1.94 mL, 2.13 g, 12.0 mmol, 1.20 eq.) and methyl 4-acetylbenzoate (1.78 g, 10.0 mmol, 1.00 eq.). The residue was filtered over a plug of silica ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 5$  cm, pentane: $\text{Et}_2\text{O}$  (1:1)), all volatiles evaporated under reduced pressure and the residue recrystallized from a mixture of pentane: $\text{Et}_2\text{O}$  ((1:1), 80 mL, 1.50 g) at  $-25^\circ\text{C}$ . Impurity of the corresponding ethylester was detected. The obtained crystals were dissolved in MeOH (35 mL) and DMAP (10 mg) was added. The solution was stirred for 2 h at reflux. The solvent was evaporated and the residue filtered over a plug of silica ( $d \times h$ :  $2 \times 2$  cm, pentane: $\text{Et}_2\text{O}$  (1:1)) to afford the product (710 mg, 3.53 mmol, 35%) as a colorless solid.

$\text{C}_{12}\text{H}_{11}\text{NO}_2$  (201.22 g/mol):

**MP:** 102–104  $^\circ\text{C}$ .

**TLC:**  $R_f$  = 0.29 ( $\text{SiO}_2$ , pentane: $\text{Et}_2\text{O}$  (1:10), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.05 (d,  $^3J_{\text{HH}}$  = 8.6 Hz, 2H, ar-*H*), 7.51 (d,  $^3J_{\text{HH}}$  = 8.5 Hz, 2H, ar-*H*), 5.68 (s, 1H, C=CH), 3.92 (s, 3H,  $\text{OCH}_3$ ), 2.48 (s, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 168.5 (s, C=O), 158.7 (s, C=CH), 139.9 (s, ar- $q\text{C}$ ), 133.6 (s, ar- $q\text{C}$ ), 126.7 (s, ar-C), 119.5 (s, ar-C), 117.8 (s,  $\text{C}\equiv\text{N}$ ), 94.4 (s, C=CH), 24.7 (s,  $\text{CH}_3$ ), 20.0 (s,  $\text{CH}_3$ ).

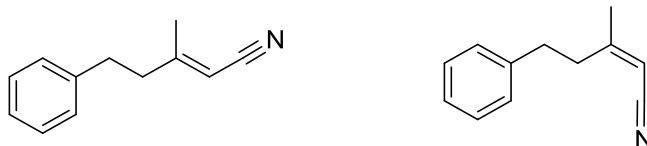
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3078 (w), 3001 (w), 2956 (w), 2207 (m), 1934 (w), 1795 (w), 1709 (s), 1608 (m), 1567 (m), 1435 (m), 1376 (w), 1339 (w), 1281 (s), 1192 (m), 1110 (m), 1014 (w), 962 (w), 829 (m), 763 (s), 693 (m).

**MS** (EI, 70 eV, 200  $^\circ\text{C}$ )  $m/z$  (%): 201.1 (40), 171.1 (13), 170.1 (100), 142.1 (26), 116.0 (10), 115.1 (24).

**EA** ( $\text{C}_{12}\text{H}_{11}\text{NO}_2$ ): calc.: C 71.63, H 5.51, N 6.96; found: C 71.64, H 5.51, N 7.08.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100  $^\circ\text{C}$  – 2 min – 7  $^\circ\text{C}/\text{min}$  – 250  $^\circ\text{C}$  – 10 min):  $t_R$  = 25.22 min.

**HPLC:** Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25  $^\circ\text{C}$ , 233 nm):  $t_R$  = 30.3 min.

**(E)-3-Methyl-5-phenylpent-2-enenitrile ((E)-6.68) and (Z)-3-methyl-5-phenylpent-2-enenitrile ((Z)-6.69)**

The  $\alpha,\beta$ -unsaturated nitriles were synthesized according to general procedure **GP9** using NaH (584 mg, 14.6 mmol, 1.50 eq., 60% in mineral oil) in THF (40 mL), diethyl cyanomethylphosphonate (1.89 mL, 2.07 g, 11.7 mmol, 1.20 eq.), benzylacetone (1.44 g, 1.46 mL, 9.74 mmol, 1.00 eq.). Filtration over a plug of silica ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 5$  cm, pentane:Et<sub>2</sub>O (10:1)) afforded a mixture of (*E/Z*)-isomers (1.53 g, 8.93 mmol, 92%, ratio (2:1)) as a colorless liquid. The isomers (1.35 g) were separated using semipreparative HPLC (OD, hexane:iso-propanol (94:6), 25 °C, 8 mL/min, 220 nm, 150 mg/injection) to afford the products ((*E*), 550 mg, 3.18 mmol, 33%) and ((*Z*), 400 mg, 2.34 mmol, 24%) both as a colorless liquids.

**(E)-3-Methyl-5-phenylpent-2-enenitrile**

$\text{C}_{12}\text{H}_{13}\text{N}$  (171.24 g/mol):

**TLC:**  $R_f$  = 0.32 ( $\text{SiO}_2$ , cyclohexane:Et<sub>2</sub>O (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.34-7.26 (m, 2H, ar-*H*), 7.25-7.18 (m, 1H, ar-*H*), 7.17-7.12 (m, 2H, ar-*H*), 5.08-5.06 (m, 1H, C=CH), 2.77 (t,  $^3J_{\text{HH}}$  = 8.2 Hz, 2H, CH<sub>2</sub>), 2.48 (t,  $^3J_{\text{HH}}$  = 8.2 Hz, 2H, CH<sub>2</sub>), 2.07 (d,  $^4J_{\text{HH}}$  = 1.2 Hz, 3H, CH<sub>3</sub>).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 164.2 (s, C=CH), 140.2 (s, ar-*qC*), 128.6 (s, ar-*C*), 128.2 (s, ar-*C*), 126.5 (s, ar-*C*), 117.1 (s, C $\equiv$ N), 95.8 (s, C=CH), 40.2 (s, CH<sub>2</sub>), 33.5 (s, CH<sub>2</sub>), 21.2 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 171.1 (13), 91.1 (100), 65.1 (10).

**Chiral GC** ( $\beta$ -Cyclodextrin, DEtTButSil (Brebhühler, SE54), (25 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (50 °C – 0 min – 20 °C/min – 108 °C – 60 min – 5 °C/min – 180 °C – 5 min):  $t_R$  = 69.0 min.

**semi-preparative HPLC:** (Daicel Chiralcel OD, hexane/*i*-PrOH = 94:6, 8.0 mL/min, 25 °C, 300 mL, 450 mg/mL):  $t_R$  = 51 min.

Obtained data are in accordance with literature data.<sup>[66]</sup>

**(Z)-3-Methyl-5-phenylpent-2-enenitrile**

$C_{12}H_{13}N$  (171.24 g/mol):

**TLC:**  $R_f$  = 0.32 (SiO<sub>2</sub>, cyclohexane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.35-7.28 (m, 2H, ar-*H*), 7.26-7.18 (m, 3H, ar-*H*), 5.10 (d,  $^4J_{HH}$  = 1.6 Hz, 1H, C=CH), 2.85-2.80 (m, 2H, CH<sub>2</sub>), 2.75-2.66 (m, 2H, CH<sub>2</sub>), 1.90 (d,  $^4J_{HH}$  = 1.6 Hz, 3H, CH<sub>3</sub>).

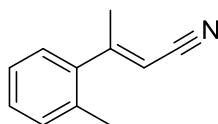
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 164.2 (s, C=CH), 140.2 (s, ar-*qC*), 128.6 (s, ar-*C*), 128.2 (s, ar-*C*), 126.5 (s, ar-*C*), 117.1 (s, C $\equiv$ N), 95.8 (s, C=CH), 40.2 (s, CH<sub>2</sub>), 33.5 (s, CH<sub>2</sub>), 21.2 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 171.1 (11), 91.1 (100), 65.1 (10).

**Chiral GC** ( $\beta$ -Cyclodextrin, DEtTButSil (Brechtbühler, SE54), (25 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (50 °C – 0 min – 20 °C/min – 108 °C – 60 min – 5 °C/min – 180 °C – 5 min):  $t_R$  = 44.2 min.

**semi-preparative HPLC:** (Daicel Chiralcel OD, hexane/*i*-PrOH = 94:6, 8.0 mL/min, 25 °C, 300 mL, 450 mg/mL):  $t_R$  = 26 min.

Obtained data are in accordance with literature data.<sup>[66]</sup>

**(E)-3-(*o*-Tolyl)but-2-enenitrile (6.44)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (893 mg, 22.3 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (2.89 mL, 3.16 g, 17.9 mmol, 1.20 eq.) and 2'-methylacetophenone (1.95 mL, 2.00 g, 14.9 mmol, 1.00 eq.). The reaction mixture was stirred for 3 h after the addition of the ketone. Purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 5  $\times$  22 cm, pentane:Et<sub>2</sub>O (30:1)) afforded the product (1.21 g, 7.70 mmol, 52%) as a colorless liquid.

$C_{11}H_{11}N$  (157.22 g/mol):

**TLC:**  $R_f$  = 0.53 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.28-7.08 (m, 3H, ar-*H*), 7.01-6.93 (m, 1H, ar-*H*), 5.22 (q,  $^4J_{HH}$  = 1.2 Hz, 1H, C=CH), 2.36 (d,  $^4J_{HH}$  = 1.2 Hz, 3H, CH<sub>3</sub>), 2.29 (s, 3H, CH<sub>3</sub>).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 163.4 (s,  $\text{C}=\text{CH}$ ), 140.5 (s, ar- $_{\text{q}}\text{C}$ ), 134.0 (s, ar- $_{\text{q}}\text{C}$ ), 130.8 (s, ar- $\text{C}$ ), 128.7 (s, ar- $\text{C}$ ), 127.0 (s, ar- $\text{C}$ ), 126.0 (s, ar- $\text{C}$ ), 116.8 (s,  $\text{C}\equiv\text{N}$ ), 99.1 (s,  $\text{C}=\text{CH}$ ), 23.0 (s,  $\text{CH}_3$ ), 19.8 (s,  $\text{CH}_3$ ).

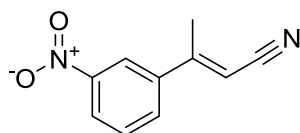
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 158.1 (11), 157.1 (92), 156.1 (34), 140.1 (10), 131.1 (12), 130.1 (100), 129.1 (82), 128.1 (17), 127.1 (10), 116.1 (17), 115.1 (84), 91.1 (14).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_{\text{R}}$  = 16.15 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 92:08, 0.5 mL/min, 25 °C, 208 nm):  $t_{\text{R}}$  = 12.9 min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

### (*E*)-3-(3-Nitrophenyl)but-2-enitrile (6.63)



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.28 g, 18.5 mmol, 1.20 eq.) and 3'-nitroacetophenone (2.63 g, 15.5 mmol, 1.00 eq.). Purification by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 5  $\times$  26 cm, cyclohexane:ethyl acetate (1:1)) afforded the product (950 mg, 13.4 mmol, 33%) as a colorless solid.

$\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2$  (188.19 g/mol):

**MP**: 88-90 °C.

**TLC**:  $R_f$  = 0.34 ( $\text{SiO}_2$ , cyclohexane:ethyl acetate (5:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.34-8.22 (m, 2H, ar- $H$ ), 7.79 (d,  $^3J_{\text{HH}}$  = 7.9 Hz, 1H, ar- $H$ ), 7.62 ("t",  $^3J_{\text{HH}}$  = 8.0 Hz, 1H, ar- $H$ ), 5.74 (s, 1H,  $\text{C}=\text{CH}$ ), 2.54 (s, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 157.3 (s,  $\text{C}=\text{CH}$ ), 148.8 (s, ar- $_{\text{q}}\text{C}$ ), 140.1 (s, ar- $_{\text{q}}\text{C}$ ), 131.8 (s, ar- $\text{C}$ ), 130.3 (s, ar- $\text{C}$ ), 124.9 (s, ar- $\text{C}$ ), 121.1 (s, ar- $\text{C}$ ), 116.8 (s,  $\text{C}\equiv\text{N}$ ), 98.6 (s,  $\text{C}=\text{CH}$ ), 20.5 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3092 (w), 2985 (w), 2867 (w), 2214 (m), 2214 (m), 1611 (w), 1517 (s), 1433 (w), 1354 (s), 1114 (w), 1020 (w), 949 (w), 904 (w), 872 (m), 834 (m), 736 (m), 678 (m).

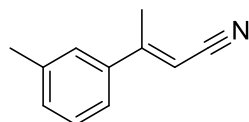
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 189.1 (12), 188.1 (100), 158.2 (15), 143.1 (13), 142.1 (12), 141.1 (12), 140.1 (29), 130.1 (20), 116.1 (35), 115.1 (80), 103.1 (20), 89.1 (19), 63.1 (14), 51.0 (10).

**EA** (C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>): calc.: C 63.82, H 4.28, N 14.89; found: C 63.71, H 4.34, N 15.10.

**GC-MS** (Restek Rtx-5MS (30 m × 0.25 mm × 0.25 μm) 100 kPa He (50 °C – 2 min – 30 °C/min – 250 °C – 5 min):  $t_R$  = 9.11 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 94:06, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 45.9 min.

**(E)-3-(*m*-Tolyl)but-2-enenitrile (6.47)**



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.28 g, 18.5 mmol, 1.20 eq.) and 3'-methylacetophenone (2.14 g, 2.17 mL, 15.5 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 24 cm, pentane:Et<sub>2</sub>O (50:1)) afforded the product (2.11 g, 13.4 mmol, 87%) as a colorless liquid.

C<sub>11</sub>H<sub>11</sub>N (157.22 g/mol):

**TLC**:  $R_f$  = 0.41 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (50:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.37-7.13 (m, 4H, ar-*H*), 5.74-5.43 (m, 1H, C=CH), 2.45 (d, <sup>4</sup> $J_{HH}$  = 1.1 Hz, 3H, CH<sub>3</sub>), 2.38 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 160.0 (s, C=CH), 138.6 (s, ar-<sub>q</sub>C), 138.3 (s, ar-<sub>q</sub>C), 131.1 (s, ar-C), 128.8 (s, ar-C), 126.6 (s, ar-C), 123.1 (s, ar-C), 117.8 (s, C≡N), 95.4 (s, C=CH), 21.5 (s, CH<sub>3</sub>), 20.3 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3047 (w), 2958 (w), 2923 (w), 2213 (s), 1602 (m), 1582 (m), 1441 (m), 1380 (w), 1329 (w), 1278 (w), 1196 (w), 1103 (w), 1041 (w), 881 (w), 826 (w), 781 (s), 695 (s), 634 (s).

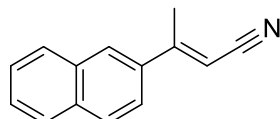
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 158.1 (13), 157.1 (100), 156.1 (84), 143.1 (10), 140.1 (12), 130.1 (17), 129.1 (39), 128.1 (18), 116.1 (11), 115.1 (42), 92.1 (11), 91.1 (21), 65.1 (10).

**HRMS** (EI): ( $m/z$ ) calc. for C<sub>11</sub>H<sub>11</sub>N<sup>+</sup>: 157.0886 [M]<sup>+</sup>; found: 157.0884.

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 18.27 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 15.5 min.

**(E)-3-(Naphthalen-2-yl)but-2-enenitrile (6.62)**



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (930 mg, 23.3 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.01 mL, 3.29 g, 18.6 mmol, 1.20 eq.) and 2-acetonaphthone (2.66 g, 15.5 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 25 cm, pentane:Et<sub>2</sub>O (20:1)) afforded the product (1.72 g, 8.90 mmol, 58%) as a colorless solid.

C<sub>14</sub>H<sub>11</sub>N (193.25 g/mol):

**MP**: 60-61 °C.

**TLC**:  $R_f$  = 0.27 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (20:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.93 (s br, 1H, ar-*H*), 7.90-7.82 (m, 3H, ar-*H*), 7.58-7.52 (m, 3H, ar-*H*), 5.76 (q, <sup>4</sup> $J_{HH}$  = 1.1 Hz, 1H, C=CH), 2.58 (d, <sup>4</sup> $J_{HH}$  = 1.1 Hz, 3H, CH<sub>3</sub>).

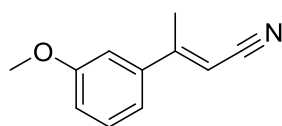
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 159.4 (s, C=CH), 135.4 (s, ar-*qC*), 134.1 (s, ar-*qC*), 133.0 (s, ar-*qC*), 128.8 (s, ar-*C*), 128.7 (s, ar-*C*), 127.8 (s, ar-*C*), 127.5 (s, ar-*C*), 127.1 (s, ar-*C*), 126.2 (s, ar-*C*), 122.9 (s, ar-*C*), 117.8 (s, C≡N), 95.9 (s, C=CH), 20.3 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 194.1 (16), 193.1 (100), 192.1 (16), 165.1 (17), 151.1 (10), 128.1 (26).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 28.36 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 92:08, 0.5 mL/min, 25 °C, 276 nm):  $t_R$  = 24.7 min.

Obtained data are in accordance with literature data.<sup>[148]</sup>

**(E)-3-(3-Methoxyphenyl)but-2-enenitrile (6.49)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (930 mg, 23.3 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.01 mL, 3.29 g, 18.6 mmol, 1.20 eq.) and 3'-methoxyacetophenone (2.33 g, 2.14 mL, 15.5 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 5  $\times$  25 cm, pentane:Et<sub>2</sub>O (20:1)) afforded the product (1.95 g, 11.3 mmol, 73%) as a colorless liquid.

C<sub>11</sub>H<sub>11</sub>NO (173.21 g/mol):

**TLC:** R<sub>f</sub> = 0.21 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (20:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.37-7.27 (m, 1H, ar-*H*), 7.07-7.00 (m, 1H, ar-*H*), 7.00-6.91 (m, 2H, ar-*H*), 5.60 (s, 1H, C=CH), 3.83 (s, 3H, OCH<sub>3</sub>), 2.44 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 159.8 (s, ar-<sub>q</sub>C), 159.7 (s, C=CH), 139.7 (s, ar-<sub>q</sub>C), 129.9 (s, ar-C), 118.3 (s, ar-C), 117.6 (s, C $\equiv$ N), 115.3 (s, ar-C), 111.9 (s, ar-C), 95.8 (s, C=CH), 55.4 (s, OCH<sub>3</sub>), 20.3 (s, CH<sub>3</sub>).

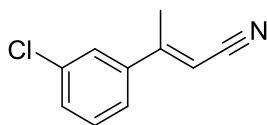
**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3069 (w), 2961 (w), 2838 (w), 2213 (s), 1614 (m), 1577 (s), 1487 (m), 1430 (m), 1381 (w), 1328 (m), 1288 (s), 1216 (s), 1043 (s), 824 (w), 779 (s), 691 (m), 629 (s).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 174.1 (12), 173.1 (100), 172.1 (10), 158.1 (17), 145.1 (22), 144.1 (26), 143.1 (14), 130.1 (13), 116.1 (16), 115.1 (18), 108.1 (20), 103.1 (25), 78.1 (11), 77.1 (19).

**EA** (C<sub>11</sub>H<sub>11</sub>N): calc.: C 76.28, H 6.40, N 8.09; found: C 76.11, H 6.33, N 8.31.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 21.30 min.

**HPLC:** Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 92:08, 0.5 mL/min, 25 °C, 217 nm): t<sub>R</sub> = 39.4 min (overlay with first enantiomers of the hydrogenation product).

**(E)-3-(3-Chlorophenyl)but-2-enenitrile (6.51)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (970 mg, 24.3 mmol, 1.50 eq., 60% in mineral oil) in THF (50 mL), diethyl cyanomethylphosphonate (3.14 mL, 3.44 g, 19.4 mmol, 1.20 eq.) and 3'-chloroacetophenone (2.50 g, 2.10 mL, 16.2 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 5  $\times$  25 cm, pentane:Et<sub>2</sub>O (40:1)) afforded the product (900 mg, 5.07 mmol, 31%) as a colorless solid.

C<sub>10</sub>H<sub>8</sub>ClN (177.63 g/mol):

**MP:** 29-30 °C.

**TLC:** R<sub>f</sub> = 0.45 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.46-7.30 (m, 4H, ar-*H*), 5.62 (s, 1H, C=CH), 2.45 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 158.4 (s, C=CH), 140.1 (s, ar-*qC*), 135.1 (s, ar-*qC*), 130.3 (s, ar-*C*), 130.2 (s, ar-*C*), 126.2 (s, ar-*C*), 124.1 (s, ar-*C*), 117.2 (s, C $\equiv$ N), 97.0 (s, C=CH), 20.3 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3064 (w), 2994 (w), 2213 (s), 1994 (w), 1870 (w), 1794 (w), 1682 (w), 1605 (m), 1563 (m), 1420 (s), 1381 (m), 1324 (w), 1089 (m), 1013 (w), 937 (w), 896 (w), 833 (s), 771 (s), 700 (s).

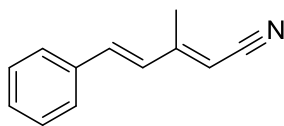
**MS** (EI, 70 eV, 200 °C) *m/z* (%): 179.0 (32), 178.1 (12), 177.0 (100), 142.1 (58), 140.1 (19), 137.1 (13), 116.1 (13), 115.1 (75), 114.1 (19), 112.0 (32), 102.1 (11), 75.0 (15).

**EA** (C<sub>10</sub>H<sub>8</sub>ClN): calc.: C 67.62, H 4.54, N 7.89; found: C 67.65, H 4.58, N 7.94.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 20.26 min.

**HPLC:** Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 220 nm): t<sub>R</sub> = 24.0 min.



**(2E,4E)-3-Methyl-5-phenylpenta-2,4-dienenitrile (6.67)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.28 g, 18.5 mmol 1.20 eq.) and (*E*)-4-phenylbut-3-en-2-one (2.62 g, 15.5 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 25 cm, pentane:Et<sub>2</sub>O (25:1)) afforded the product as (*E/Z*)-mixture (4:1) (704 mg, 4.16 mmol, 27%) as a colorless solid. Double recrystallization from pentane:Et<sub>2</sub>O afforded the pure (*E*) isomere (180 mg, 1.06 mmol, 7%).

C<sub>12</sub>H<sub>11</sub>N (169.23 g/mol):

**MP:** 65-66 °C.

**TLC:** R<sub>f</sub> = 0.35 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.51-7.44 (m, 2H, ar-*H*), 7.43-7.29 (m, 3H, ar-*H*), 6.91 (d, <sup>3</sup>J<sub>HH</sub> = 16.1 Hz, 1H, HC=CH), 6.82 (d, <sup>3</sup>J<sub>HH</sub> = 16.0 Hz, 1H, HC=CH), 5.32 (s, 1H, C=CH), 2.27 (s, 3H, CH<sub>3</sub>).

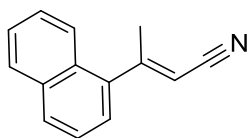
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 156.8 (s, C=CH), 136.0 (s, ar-<sub>q</sub>C), 135.7 (s, C<sub>6</sub>H<sub>5</sub>HC=CH), 129.4 (s, ar-C), 129.0 (s, ar-C), 128.4 (s, C<sub>6</sub>H<sub>5</sub>HC=CH), 127.4 (s, ar-C), 117.9 (s, C≡N), 98.2 (s, CHC≡N), 16.8 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3259 (w), 3080 (w), 3016 (w), 2206 (m), 1990 (w), 1915 (w), 1823 (w), 1722 (w), 1677 (w), 1617 (m), 1582 (m), 1492 (m), 1434 (m), 1331 (m), 1195 (m), 1029 (w), 962 (s), 846 (m), 804 (s), 752 (s), 693 (s).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 169.1 (48), 168.1 (15), 155.1 (12), 154.1 (100), 153.1 (14), 141.1 (13), 127.1 (33).

**EA** (C<sub>12</sub>H<sub>11</sub>N): calc.: C 85.17, H 6.55, N 8.28; found: C 85.30, H 6.71, N 8.32.

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 22.89 min.

**(E)-3-(Naphthalen-1-yl)but-2-enenitrile (6.45)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 23.3 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.29 g, 18.5 mmol, 1.20 eq.) and 1-acetonaphthone (2.77 g, 2.47 mL, 15.5 mmol, 1.00 eq.). Purification by column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 20$  cm, pentane:Et<sub>2</sub>O (20:1)) afforded the product (1.63 g, 8.43 mmol, 55%) as a colorless solid.

$\text{C}_{14}\text{H}_{11}\text{N}$  (193.25 g/mol):

**MP:** 51-52 °C.

**TLC:**  $R_f = 0.34$  ( $\text{SiO}_2$ , pentane:Et<sub>2</sub>O (17:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 7.93\text{--}7.81$  (m, 3H, ar-*H*), 7.58-7.51 (m, 2H, ar-*H*), 7.47 (dd,  $^3J_{\text{HH}} = 8.3$  Hz,  $^3J_{\text{HH}} = 7.0$  Hz, 1H, ar-*H*), 7.29 (dd,  $J = 7.1, 1.3$  Hz, 1H, ar-*H*), 5.46 (d,  $^3J_{\text{HH}} = 1.3$  Hz, 1H, C=CH), 2.56 (d,  $^3J_{\text{HH}} = 1.3$  Hz, 3H,  $\text{CH}_3$ ).

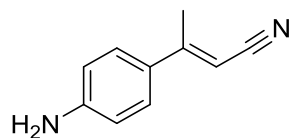
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 162.3$  (s, C=CH), 138.6 (s, ar- $q\text{C}$ ), 133.7 (s, ar- $q\text{C}$ ), 129.8 (s, ar- $q\text{C}$ ), 129.3 (s, ar- $q\text{C}$ ), 128.7 (s, ar- $q\text{C}$ ), 126.9 (s, ar- $q\text{C}$ ), 126.4 (s, ar- $q\text{C}$ ), 125.1 (s, ar- $q\text{C}$ ), 124.7 (s, ar- $q\text{C}$ ), 124.4 (s, ar- $q\text{C}$ ), 116.8 (s, C $\equiv$ N), 100.2 (s, C=CH), 23.8 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1} = 3058$  (w), 3043 (w), 2981 (w), 2218 (m), 1624 (w), 1589 (w), 1508 (w), 1431 (m), 1395 (m), 1373 (w), 1316 (w), 1248 (w), 1207 (w), 1068 (w), 1029 (w), 846 (m), 830 (w), 804 (s), 774 (s), 744 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 194.1 (17), 193.1 (100), 192.1 (16), 165.1 (18), 151.1 (11), 128.1 (29).

**EA** ( $\text{C}_{14}\text{H}_{11}\text{N}$ ): calc.: C 87.01, H 5.74, N 7.25; found: C 86.77, H 5.81, N 7.35.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R = 24.88$  min.

**(E)-3-(4-Aminophenyl)but-2-enenitrile (6.66)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (988 mg, 24.7 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.20 mL, 3.50 g, 19.8 mmol, 1.20 eq.) and 4'-aminoacetophenon (2.27 g, 16.5 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 5  $\times$  5 cm, cyclohexane:ethyl acetate (1:1)) afforded the product as (*E/Z*)-mixture (2.08 g). Recrystallization from chloroform:hexane (1:1) afforded the (*E*)-product (1.32 g, 8.32 mmol, 51%) as a colorless solid.

C<sub>10</sub>H<sub>10</sub>N<sub>2</sub> (158.20 g/mol):

**MP:** 109-110 °C.

**TLC:** R<sub>f</sub> = 0.29 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (1:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.31 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 2H, ar-*H*), 6.65 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 2H, ar-*H*), 5.49 (s, 1H, C=CH), 3.98 (s, 2H, NH<sub>2</sub>), 2.40 (s, 3H, CH<sub>3</sub>).

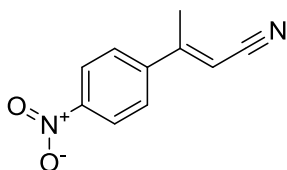
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 159.1 (s, C=CH), 148.9 (s, ar-<sub>q</sub>C), 127.7 (s, ar-C), 127.5 (s ar-<sub>q</sub>C), 118.9 (s, C $\equiv$ N), 114.7 (s, ar-C), 91.3 (s, C=CH), 19.9 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3450 (m), 3365 (m), 2198 (s), 1900 (w), 1624 (m), 1576 (s), 1434 (m), 1382 (w), 1259 (m), 1172 (m), 1144 (w), 1048 (w), 827 (s), 796 (s).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 159.1 (12), 158.1 (100), 143.1 (58), 131.1 (11), 130.1 (11), 116.1 (18), 93.1 (10).

**EA** (C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>): calc.: C 75.92, H 6.37, N 17.71; found: C 76.04, H 6.42, N 18.11.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): t<sub>R</sub> = 26.73 min.

**(E)-3-(4-Nitrophenyl)but-2-enenitrile (6.64)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (927 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (3.28 mL, 3.00 g, 18.5 mmol, 1.20 eq.) and 4'-nitroacetophenone (2.55 g, 15.5 mmol, 1.00 eq.). Extraction and filtration over a plug of silica ( $d \times h$ :  $2 \times 5$  cm, pentane:Et<sub>2</sub>O (1:1)) afforded the product as (*E/Z*)-mixture (1.85 g) as a brown solid. Recrystallization from hexane:ethyl acetate (5:1) afforded the pure (*E*)-product (1.47 g, 7.81 mmol, 51%) as a pale yellow solid.

C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub> (188.19 g/mol):

**MP**: 117-119 °C.

**TLC**:  $R_f$  = 0.64 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (1:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 8.26 (d,  $^3J_{\text{HH}}$  = 8.9 Hz, 2H, ar-*H*), 7.62 (d,  $^3J_{\text{HH}}$  = 8.9 Hz, 2H, ar-*H*), 5.72 (q,  $^4J_{\text{HH}}$  = 1.0 Hz, 1H, C=CH), 2.48 (d,  $^4J_{\text{HH}}$  = 1.0 Hz, 3H, CH<sub>3</sub>).

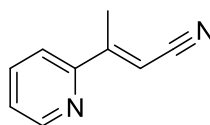
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 157.6 (s, C=CH), 148.8 (s, ar-C), 144.5 (s, ar-C), 127.1 (s, ar-C), 124.2 (s, ar-C), 116.7 (s, C≡N), 99.4 (s, C=CH), 20.5 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3078 (w), 2988 (w), 2847 (w), 2452 (w), 2215 (m), 1933 (w), 1796 (w), 1594 (m), 1512 (s), 1441 (w), 1338 (s), 1195 (w), 1111 (m), 1010 (w), 856 (s), 822 (s), 748 (s), 688 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 189.1 (11), 188.1 (100), 158.1 (26), 142.1 (41), 141.1 (10), 140.1 (26), 130.1 (18), 116.1 (32), 115.1 (70), 103.1 (41), 89.1 (18), 77.1 (14), 63.1 (14), 51.1 (10).

**EA** (C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>): calc.: C 63.82, H 4.28, N 14.89; found: C 64.06, H 4.30, N 15.21.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 27.70 min.

**(E)-3-(Pyridin-2-yl)but-2-enitrile (6.65)**

The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (773 mg, 19.3 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (2.50 mL, 2.74 g, 15.5 mmol, 1.20 eq.) and 2-acetylpyridine (1.44 mL, 1.56 g, 12.9 mmol, 1.00 eq.). Purification by column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 20$  cm, cyclohexane:ethyl acetate (1:1)) afforded the product (196 mg, 1.36 mmol, 11%) as a colorless solid.

$\text{C}_9\text{H}_8\text{N}_2$  (144.18 g/mol):

**TLC:**  $R_f = 0.55$  ( $\text{SiO}_2$ , ethyl acetate:cyclohexane (20:1), UV).

**MP:** 31–32 °C.

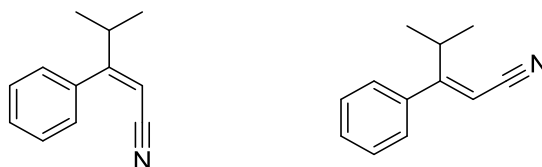
**$^1\text{H-NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 8.62$  (ddd,  $J = 4.8, 1.8, 0.9$  Hz, 1H, ar-*H*), 7.75 (td,  $J = 7.8, 1.9$  Hz, 1H, ar-*H*), 7.51 (dt,  $J = 8.0, 1.0$  Hz, 1H, ar-*H*), 7.31 (ddd,  $J = 7.7, 4.7, 1.1$  Hz, 1H, ar-*H*), 6.56 (q,  $J = 1.0$  Hz, 1H, C=CH), 2.49 (d,  $J = 1.0$  Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm} = 157.2$  (s, C=CH), 154.1 (s, ar- $q\text{C}$ ), 149.8 (s, ar-C), 137.2 (s, ar-C), 124.8 (s, ar-C), 120.8 (s, ar-C), 117.9 (s, C $\equiv$ N), 98.7 (s, C=CH), 18.6 (s,  $\text{CH}_3$ ).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 145.1 (10), 144.1 (100), 143.1 (49), 129.1 (14), 188.1 (15), 177.1 (25), 104.1 (33), 93.1 (12), 79.0 (36), 78.0 (18).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R = 17.75$  min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

**(E)-4-Methyl-3-phenylpent-2-enitrile (6.52) and (Z)-4-methyl-3-phenylpent-2-enitrile (6.53)**

The  $\alpha,\beta$ -unsaturated nitriles were synthesized according to general procedure **GP9** using NaH (927 mg, 23.2 mmol, 1.50 eq., 60% in mineral oil) in THF (40 mL), diethyl cyanomethylphosphonate (3.00 mL, 3.29 g, 18.5 mmol, 1.20 eq.) and 2-methyl-1-

phenylpropan-1-one (2.36 g, 15.5 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 25 cm, pentane:Et<sub>2</sub>O (50:1)) afforded the (*E*)-product (902 mg, 5.55 mmol, 34%) and the (*Z*)-product (500 mg, 2.92 mmol, 19%) both as a colorless liquid.

C<sub>12</sub>H<sub>13</sub>N (171.24 g/mol):

(*E*)-4-Methyl-3-phenylpent-2-enenitrile:

**TLC:** R<sub>f</sub> = 0.50 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.41-7.32 (m, 3H, ar-*H*), 7.26-7.20 (m, 2H, ar-*H*), 5.26 (s, 1H, C=CH), 3.33 (sept, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.25 (d, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 172.2 (s, C=CH), 138.9 (s, ar-*q*C), 129.0 (s, ar-*C*), 128.4 (s, ar-*C*), 127.2 (s, ar-*C*), 116.9 (s, C≡N), 96.6 (s, C=CH), 34.6 (s, CH(CH<sub>3</sub>)<sub>2</sub>), 21.3 (s, CH(CH<sub>3</sub>)<sub>2</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 171.1 (55), 170.2 (17), 157.1 (10), 156.1 (72), 129.1 (100), 128.1 (26), 127.1 (12), 116.1 (11), 155.1 (17), 102.1 (16), 91.1 (10), 78.1 (14), 77.1 (16), 51.0 (11).

(*Z*)-4-Methyl-3-phenylpent-2-enenitrile:

**TLC:** R<sub>f</sub> = 0.47 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

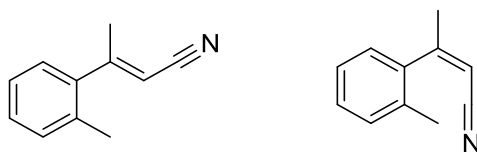
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ/ppm = 7.45-7.38 (m, 2H, ar-*H*), 7.36-7.32 (m, 2H, ar-*H*), 5.35 (d, *J* = 1.4 Hz, 1H, C=CH), 2.85 (sept, *J* = 6.8, 1.4 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.10 (d, *J* = 7.0 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 172.4 (s, C=CH), 138.3 (s, ar-*q*C), 129.3 (s, ar-*C*), 128.6 (s, ar-*C*), 127.4 (s, ar-*C*), 117.7 (s, C≡N), 94.4 (s, C=CH), 35.8 (s, CH), 21.2 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 171.2 (52), 170.1 (17), 156.1 (74), 130.1 (20), 129.1 (100), 128.1 (27), 127.1 (12), 116.1 (11), 115.1 (17), 102.1 (17), 91.1 (10), 78.1 (14), 77.1 (16).

Obtained data are in accordance with the literature data obtained by Maissey *et al.*<sup>[119]</sup> Data is not in accordance with literature data in which the (*E*)-isomer is assigned as (*Z*)-isomer.<sup>[110b]</sup>

The assignment of the configuration was confirmed by NOESY experiments.

**(*E*)-3-(*o*-Tolyl)but-2-enenitrile (6.44) and (*Z*)-3-(*o*-tolyl)but-2-enenitrile**

The  $\alpha,\beta$ -unsaturated nitriles were synthesized according to general procedure **GP9** using NaH (893 mg, 22.3 mmol, 1.50 eq., 60% in mineral oil) in THF (60 mL), diethyl cyanomethylphosphonate (2.89 mL, 3.16 g, 17.9 mmol, 1.20 eq.) and 2'-methylacetophenone (1.95 mL, 2.00 g, 14.9 mmol, 1.00 eq.). The reaction mixture was stirred for 3 h after the addition of the ketone. Purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h: 5  $\times$  22 cm, pentane:Et<sub>2</sub>O (30:1)) afforded the (*E*)-isomer (1.21 g, 7.70 mmol, 52%) and (*Z*)-isomer (640 mg, 4.01 mmol, 27%) as colorless liquids.

C<sub>11</sub>H<sub>11</sub>N (157.22 g/mol):

(*E*)-3-(*o*-Tolyl)but-2-enenitrile:

**TLC:**  $R_f$  = 0.53 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.28-7.08 (m, 3H, ar-*H*), 7.01-6.93 (m, 1H, ar-*H*), 5.22 (q, <sup>4</sup> $J_{HH}$  = 1.2 Hz, 1H, C=CH), 2.36 (d, <sup>4</sup> $J_{HH}$  = 1.2 Hz, 3H, CH<sub>3</sub>), 2.29 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 163.4 (s, C=CH), 140.5 (s, ar-<sub>q</sub>C), 134.0 (s, ar-<sub>q</sub>C), 130.8 (s, ar-C), 128.7 (s, ar-C), 127.0 (s, ar-C), 126.0 (s, ar-C), 116.8 (s, C $\equiv$ N), 99.1 (s, C=CH), 23.0 (s, CH<sub>3</sub>), 19.8 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 158.1 (11), 157.1 (92), 156.1 (34), 140.1 (10), 131.1 (12), 130.1 (100), 129.1 (82), 128.1 (17), 127.1 (10), 116.1 (17), 115.1 (84), 91.1 (14).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 16.15 min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

(*Z*)-3-(*o*-Tolyl)but-2-enenitrile:

**TLC:**  $R_f$  = 0.35 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.24-7.12 (m, 3H, ar-*H*), 7.08-6.96 (m, 1H, ar-*H*), 5.42 (q, <sup>4</sup> $J_{HH}$  = 1.6 Hz, 1H, C=CH), 2.23 (s, 3H, CH<sub>3</sub>), 2.11 (d, <sup>4</sup> $J_{HH}$  = 1.6 Hz, 3H, CH<sub>3</sub>).

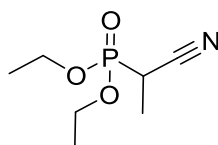
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 163.8 (s, C=CH), 138.9 (s, ar-<sub>q</sub>C), 134.0 (s, ar-<sub>q</sub>C), 130.8 (s, ar-C), 128.8 (s, ar-C), 126.8 (s, ar-C), 126.2 (s, ar-C), 116.7 (s, C $\equiv$ N), 98.7 (s, C=CH), 25.7 (s, CH<sub>3</sub>), 19.3 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 158.1 (12), 157.1 (91), 156.1 (34), 140.1 (10), 131.1 (12), 131.1 (12), 130.1 (100), 129.1 (81), 128.1 (17), 127.1 (10), 116.1 (16), 115.1 (84), 91.1 (13), 77.1 (10).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 16.64 min.

Obtained data are in accordance with literature data.<sup>[119]</sup>

### Diethyl (1-cyanoethyl)phosphonate



*n*-BuLi (2.5 M, 50.4 mL, 8.07 g, 126 mmol, 2.10 eq.) and THF (80 mL) were placed in a two-neck round bottom flask and cooled to –78 °C. Diisopropylamine (17.9 mL, 12.9 g, 128 mmol, 2.10 eq.) in THF (60 mL) was added dropwise to the stirred solution via a dropping funnel and stirring was maintained for 10 min at –78 °C. Then propionitrile (4.34 mL, 3.30 g, 60.0 mmol, 1.00 eq.) in THF (60 mL) was added dropwise at the same temperature. After 30 min diethyl chlorophosphate (9.50 mL, 10.7 g, 62.0 mmol, 1.00 eq.) in THF (60 mL) was added at –78 °C via a dropping funnel and stirring was maintained at –78 °C for 15 min. Afterwards, the reaction mixture was allowed to warm to room temperature and poured into a stirred mixture of HCl (3 M, 100 mL), CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and ice (60 g). The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  60 mL). The combined organic layers were washed with H<sub>2</sub>O (50 mL), dried over MgSO<sub>4</sub>, filtered and all volatiles were evaporated under reduced pressure to afford a yellowish liquid (6.96 g, 36.4 mmol, 61%) which showed sufficient purity for the next step.

C<sub>7</sub>H<sub>14</sub>NO<sub>3</sub>P (143.19 g/mol):

**<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 4.03 (s br, 4H, OCH<sub>2</sub>), 2.87 (m, 1H, CH), 1.34 (s br, 3H, CH<sub>3</sub>), 1.18 (s br, 6H, CH<sub>2</sub>CH<sub>3</sub>).

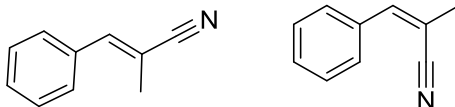
**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 117.1 (d,  $J$  = 9.4 Hz, C $\equiv$ N), 64.1 (d,  $J$  = 7.0 Hz, OCH<sub>2</sub>), 63.8 (d,  $J$  = 6.9 Hz, OCH<sub>2</sub>), 23.8 (d,  $J$  = 146 Hz, CH), 16.4 (d,  $J$  = 2.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 16.4 (d,  $J$  = 2.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 12.7 (d,  $J$  = 5.9 Hz, CHCH<sub>3</sub>).

**<sup>31</sup>P{<sup>1</sup>H} NMR** (162 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ /ppm = 18.7 (s).

Obtained data are in accordance with literature data.<sup>[149]</sup>



**(E)-2-Methyl-3-phenylacrylonitrile ((E)-6.72) and (Z)-2-methyl-3-phenylacrylonitrile ((Z)-6.73)**



NaH (60%, 780 mg, 19.5 mmol, 1.50 eq.) in THF (70 mL) was placed in a dried two-neck round bottom flask, cooled to 0 °C and diethyl cyanoethylphosphonate (2.74 mL, 2.98 g, 15.6 mmol, 1.20 eq.) was added dropwise to the stirred solution. Afterwards, the reaction mixture was allowed to warm to room temperature and stirring was maintained until gas evolution had ceased. Benzaldehyde (1.31 mL, 1.38 g, 13.0 mmol, 1.00 eq.) was added dropwise to the yellow mixture maintaining the internal temperature below 25 °C. After the addition of benzaldehyde the reaction mixture was stirred at room temperature for 17 h. EtOAc (40 mL) and H<sub>2</sub>O (80 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated under reduced pressure to afford a yellow liquid. The crude product was purified by column chromatography (SiO<sub>2</sub>, d × h: 5 × 15 cm, pentane:Et<sub>2</sub>O (45:1)) to obtain *trans*-2-methyl-3-phenylprop-2-enonitrile (0.57 g, 3.98 mmol, 31%) and *cis*-2-methyl-3-phenylprop-2-enonitrile (0.35 g, 2.45 mmol, 19%) both as a pale yellow liquid.

C<sub>10</sub>H<sub>9</sub>N (143.19 g/mol):

(E)-2-Methyl-3-phenylacrylonitrile:

**TLC:** R<sub>f</sub> = 0.26 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (45:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.38 (m, 5H, ar-*H*), 7.21 (q, <sup>4</sup>J<sub>HH</sub> = 1.5 Hz, 1H, C=CH), 2.15 (d, <sup>4</sup>J<sub>HH</sub> = 1.5 Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 144.6 (s, CH=C), 134.3 (s, ar-*qC*), 129.5 (s, ar-*C*), 129.5 (s, ar-*C*), 128.9 (s, ar-*C*), 121.4 (s, C≡N), 109.8 (s, CH=C), 17.0 (s, CH<sub>3</sub>).

(Z)-2-Methyl-3-phenylacrylonitrile:

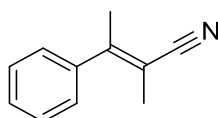
**TLC:** R<sub>f</sub> = 0.29 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (45:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.93-7.55 (m, 2H, ar-*H*), 7.39 (m, 3H, ar-*H*), 6.94 (q, <sup>4</sup>J<sub>HH</sub> = 1.6 Hz, 1H, CH=C), 2.16 (d, <sup>4</sup>J<sub>HH</sub> = 1.6 Hz, 3H, CH<sub>3</sub>).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 144.2 (s,  $\text{CH}=\text{C}$ ), 134.0 (s, ar- $_{\text{q}}\text{C}$ ), 130.0 (s, ar-C), 129.0 (s, ar-C), 128.6 (s, ar-C), 119.4 (s,  $\text{C}\equiv\text{N}$ ), 106.3 (s,  $\text{CH}=\text{C}$ ), 22.4 (s,  $\text{CH}_3$ ).

Obtained data are in accordance with literature data.<sup>[150]</sup>

**(E)-2-Methyl-3-phenylbut-2-enenitrile (6.75)**



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (780 mg, 19.5 mmol, 1.50 eq., 60% in mineral oil) in THF (70 mL), diethyl (1-cyanoethyl)phosphonate (2.74 mL, 2.97 g, 15.6 mmol, 1.20 eq.) and acetophenone (1.52 mL, 1.56 g, 13.0 mmol, 1.00 eq.). Purification by column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 15$  cm, pentane: $\text{Et}_2\text{O}$  (15:1)) afforded the product (830 mg, 5.28 mmol, 41%) as a colorless liquid.

$\text{C}_{11}\text{H}_{11}\text{N}$  (157.22 g/mol):

**TLC**:  $R_f$  = 0.15 ( $\text{SiO}_2$ , pentane: $\text{Et}_2\text{O}$  (15:1), UV).

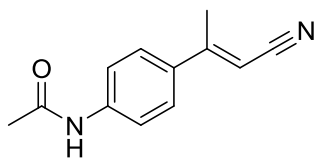
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.36 (m, 3H, ar-H), 7.15 (m, 2H, ar-H), 2.36 (q,  $^5J_{\text{HH}}$  = 1.6 Hz, 3H,  $\text{CH}_3$ ), 1.84 (q,  $^5J_{\text{HH}}$  = 1.5 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 154.4 (s, ar-C=C), 139.4 (s, ar- $_{\text{q}}\text{C}$ ), 128.7 (s, ar-C), 128.5 (s, ar-C), 127.3 (s, ar-C), 120.0 (s,  $\text{C}\equiv\text{N}$ ), 105.9 (s, ar-C=C), 24.9 (s,  $\text{CH}_3$ ), 17.8 (s,  $\text{CH}_3$ ).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 158.1 (12), 157.1 (100), 156.1 (72), 142.1 (36), 140.1 (11), 130.1 (25), 129.1 (39), 128.1 (13), 116.1 (14), 115.1 (57), 103.1 (19), 78.0 (16), 77.1 (17), 51.0 (15).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 15.34 min.

Obtained data are in accordance with literature data.<sup>[151]</sup>

**(*E*)-*N*-(4-(1-Cyanoprop-1-en-2-yl)phenyl)acetamide (6.59)**

To a solution of (*E*)-3-(4-aminophenyl) but-2-enenitrile (200 mg, 1.26 mmol, 1.00 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added acetic anhydride (125 μL, 1.33 mmol, 1.05 eq.) and *N,N*-diisopropylethylamine (209 μL, 1.26 mmol, 1.00 eq.). The reaction mixture was stirred for 2 h at room temperature and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added. The reaction mixture was washed with a saturated NaHCO<sub>3</sub> solution (3 × 10 mL) and the organic layer was dried over MgSO<sub>4</sub>. Filtration and evaporation of all volatiles afforded the product (240 mg, 1.20 mmol, 95%) as a pale yellow solid.

C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O (200.24 g/mol):

**MP:** 171-172 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.57 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.8 Hz, 2H, ar-*H*), 7.56 (s br, 1H, NH), 7.43 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.7 Hz, 2H, ar-*H*), 5.58 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.0 Hz, 1H, C=CH), 2.44 (d, <sup>4</sup>*J*<sub>HH</sub> = 0.9 Hz, 3H, CH<sub>3</sub>), 2.20 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 168.5 (s, C=O), 158.7 (s, C=CH), 139.9 (s, ar-<sub>q</sub>C), 133.6 (s, ar-<sub>q</sub>C), 126.7 (s, ar-C), 119.5 (s, ar-C), 117.8 (s, C≡N), 94.4 (s, C=CH), 24.7 (s, CH<sub>3</sub>), 20.0 (s, CH<sub>3</sub>).

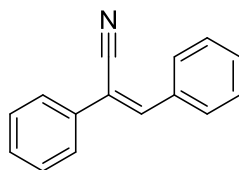
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3317 (m), 3189 (w), 3107 (w), 3045 (m), 2854 (w), 2210 (m), 1684 (s), 1586 (s), 1530 (s), 1412 (m), 1370 (m), 1324 (m), 1270 (s), 1191 (m), 1016 (w), 814 (s), 728 (m).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 200.1 (36), 159.1 (12), 158.1 (100), 143.1 (30), 43 (21).

**EA** (C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O): calc.: C 71.98, H 6.04, N 13.99; found: C 71.68, H 6.05, N 19.87.

**GC** (Optima 5 (30 m × 0.25 mm × 0.5 μm) 60 kPa He (150 °C – 0 min – 10 °C/min – 250 °C – 20 min)): *t*<sub>R</sub> = 21.94 min.

**HPLC:** Daicel, Chiralpak IC (0.46 cm × 25 cm, heptane/iso-propanol = 80:20, 0.5 mL/min, 25 °C, 246 nm): *t*<sub>R</sub> = 51.6 min.

**(Z)-2,3-Diphenylacrylonitrile (6.2)**

A mixture of benzaldehyde (1.11 mL, 1.17 g, 11.0 mmol, 1.00 eq.), phenylacetonitrile (11.0 mmol, 1.00 eq.), and  $K_2CO_3$  (1.69 g, 13.2 mmol, 1.20 eq.) in MeOH (50 mL) was stirred for 4 h at reflux under an argon atmosphere. The reaction mixture was cooled to 0 °C, the precipitate was collected by filtration, washed with  $H_2O$  (25 mL) and pentane (25 mL). Drying in HV afforded (Z)-2,3-diphenylacrylonitrile (1.62 g, 7.91 mmol, 72%) as a colorless solid.

$C_{15}H_{11}N$  (143.19 g/mol):

**MP:** 84-85 °C.

**TLC:**  $R_f$  = 0.19 ( $SiO_2$ , pentane:Et<sub>2</sub>O (35:1), UV).

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 7.91-7.89 (m, 2H, ar-H), 7.70-7.67 (m, 2H, ar-H), 7.55 (s, 1H, C=CH), 7.51-7.35 (m, 6H, ar-H).

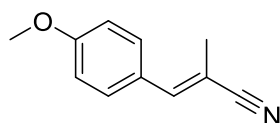
**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 142.5 (s, C=CH), 134.7 (s, ar-<sub>q</sub>C), 133.9 (s, ar-<sub>q</sub>C), 130.7 (s, ar-C), 129.5 (s, ar-C), 129.4 (s, ar-C), 129.3 (s, ar-C), 129.2 (s, ar-C), 126.2 (s, ar-C), 118.2 (s, C≡N), 111.9 (s, C=CH).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 206.1 (15), 205.0 (100), 204.0 (80), 203.0 (21), 190.0 (42), 178.1 (17), 177.0 (20), 176.0 (16), 102.1 (10), 89.1 (20), 88.1 (14), 76.0 (11).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 27.80 min.

**HPLC:** Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min, 20 °C, 220nm):  $t_R$  = 16.2 min.

Obtained data are in accordance with literature data.<sup>[152]</sup>

**(E)-3-(4-Methoxyphenyl)-2-methylacrylonitrile (6.1)**

A mixture of 4-methoxybenzenediazonium tetrafluoroborate (1.00 g, 4.51 mmol, 1.00 eq.), methyl acrylonitrile (300 mg, 373  $\mu$ L, 4.51 mmol, 1.00 eq.), palladium diacetate (20 mg,

2 mol%) and  $\text{CaCO}_3$  (451 mg, 4.51 mmol, 1.00 eq.) in MeOH (15 mL) was stirred for 16 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography ( $\text{SiO}_2$ , d  $\times$  h: 3  $\times$  20 cm, pentane:Et<sub>2</sub>O (10:1)) to afford the product as a colorless solid (275 mg, 1.59 mmol, 35%).

$\text{C}_{11}\text{H}_{11}\text{NO}$  (173.21 g/mol):

**MP:** 35-36 °C.

**TLC:**  $R_f$  = 0.28 ( $\text{SiO}_2$ , pentane:Et<sub>2</sub>O (10:1), UV).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm = 7.68 (d,  $^3J_{\text{HH}}$  = 8.8 Hz, 2H, ar-*H*), 6.92 (d,  $^3J_{\text{HH}}$  = 8.8 Hz, 2H, ar-*H*), 6.85 (s, 1H, C=CH), 3.84 (s, 3H, OCH<sub>3</sub>), 2.12 (s, 3H, CH<sub>3</sub>).

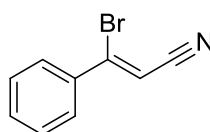
**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta$ /ppm = 160.8 (s, ar-*qC*), 143.7 (s, C=CH), 130.0 (s, ar-*C*), 126.7 (s, ar-*qC*), 119.8 (s, C $\equiv$ N), 114.2 (s, ar-*C*), 103.0 (s, C=CH), 55.4 (s, OCH<sub>3</sub>), 22.1 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3027 (w), 2970 (w), 2840 (w), 2205 (s), 2043 (w), 1900 (w), 1602 (s), 1510 (s), 1441 (m), 1368 (w), 1303 (m), 1255 (s), 1217 (w), 1184 (s), 1155 (w), 1114 (w), 1030 (s), 1016 (m), 903 (s), 826 (s), 781 (w), 623 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 174.1 (12), 173.1 (100), 172.1 (13), 158.1 (21), 13.1 (30), 121.1 (16), 115.1 (11), 103.1 (41), 77.1 (21).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 21.16 min.

### (*Z*)-3-bromo-3-phenylacrylonitrile (6.77)



A two-necked round bottom flask was charged with benzoylacetonitrile (0.50 g, 3.44 mmol, 1.00 eq.),  $\text{PBr}_3$  (10.1 mL, 29.0 g, 107 mmol, 31.1 eq.) and the resulting mixture was stirred for 48 h at 160 °C. The reaction mixture was cooled to room temperature and poured onto crushed ice (50 g). After the addition of  $\text{CHCl}_3$  (30 mL), the mixture was stirred for 1 h at room temperature. The organic layer was separated and aqueous layer was extracted with  $\text{CHCl}_3$  (3  $\times$  20 mL). The combined organic layers were washed with saturated  $\text{NaHCO}_3$  (2  $\times$  20 mL) and brine (25 mL) and dried over  $\text{MgSO}_4$ . The solvent was evaporated under reduced pressure to obtain a black oil. The residue was purified by column chromatography ( $\text{SiO}_2$ , d  $\times$

h:  $5 \times 10$  cm, pentane:Et<sub>2</sub>O (10:1)) to afford the product as brown oil (55.3 mg, 0.27 mmol, 8%).

C<sub>9</sub>H<sub>6</sub>BrN (208.06 g/mol):

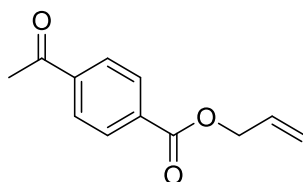
**TLC:**  $R_f$  = 0.34 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.63-7.61 (m, 2H, ar-*H*), 7.49-7.41 (m, 3H, ar-*H*), 6.23 (s, 1H, C=CH).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 145.7 (s, C-Br), 136.1 (s, ar-*qC*), 131.8 (s, ar-*C*), 128.9 (s, ar-*C*), 127.8 (s, ar-*C*), 116.7 (s, C $\equiv$ N), 100.7 (s, C=CH).

Obtained data are in accordance with literature data.<sup>[153]</sup>

### Allyl 4-acetylbenzoate



A 2 necked flask was charged with NaH (60 in mineral oil, 205 mg, 5.14 mmol, 1.10 eq.) under an argon atmosphere. A solution of 4-acetylbenzoic acid (767 mg, 4.67 mmol, 1.00 eq.) in DMF (20 mL) was added dropwise and the reaction mixture was stirred until gas evolution had ceased. Allyl bromide (592 mg, 427  $\mu$ L, 4.90 mmol, 1.05 eq.) was added and the reaction was stirred for 16 h at room temperature. H<sub>2</sub>O (100 mL) was added followed by extraction with Et<sub>2</sub>O ( $3 \times 100$  mL). The combined organic layers were dried over MgSO<sub>4</sub> and the solvent was evaporated under reduced pressure. Purification by column chromatography (SiO<sub>2</sub>, d  $\times$  h:  $10 \times 5$  cm, (pentane:Et<sub>2</sub>O (10:1)) afforded the product (620 mg, 3.04 mmol, 65%) as a colorless liquid.

C<sub>12</sub>H<sub>12</sub>O<sub>3</sub> (204.23 g/mol):

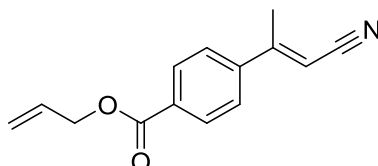
**TLC:**  $R_f$  = 0.32 (pentane:Et<sub>2</sub>O (10:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 8.17-8.07 (m, 2H, ar-*H*), 8.01-7.96 (m, 2H, ar-*H*), 6.11-5.92 (m, 1H, CH=CH<sub>2</sub>), 5.46-5.39 (m, 1H, CH=CH<sub>2</sub>), 5.34-5.24 (m, 1H, CH=CH<sub>2</sub>), 4.92-4.79 (m, 2H, OCH<sub>2</sub>), 2.63 (s, 3H, CH<sub>3</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 197.6 (s,  $\text{C}=\text{O}$ ), 165.5 (s,  $\text{CO}_2$ ), 140.4 (s,  $\text{ar-}q\text{C}$ ), 134.0 (s,  $\text{ar-}q\text{C}$ ), 132.0 (s,  $\text{C}=\text{CH}_2$ ), 130.0 (s,  $\text{ar-C}$ ), 128.3 (s,  $\text{ar-C}$ ), 118.8 (s,  $\text{C}=\text{CH}_2$ ), 66.1 (s,  $\text{OCH}_2$ ), 27.0 (s,  $\text{CH}_3$ ).

Obtained data are in accordance with literature data.<sup>[154]</sup>

**(E)-Allyl 4-(1-cyanoprop-1-en-2-yl)benzoate**



The  $\alpha,\beta$ -unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (411 mg, 10.3 mmol, 1.50 eq., 60% in mineral oil) in THF (35 mL), diethyl cyanomethylphosphonate (1.33 mL, 1.46 g, 8.23 mmol, 1.20 eq.) and allyl 4-acetylbenzoate (1.40 g, 6.86 mmol, 1.00 eq.). Purification by column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $5 \times 20$  cm, pentane: $\text{Et}_2\text{O}$  (10:1)) afforded the crude product containing 10% ethyl ester impurity (790 mg). The crude was dissolved in allylic alcohol (10 mL) followed by the addition of DBU (262 mg, 257  $\mu\text{L}$ , 1.72 mmol) and LiBr (1.49 g, 17.2 mmol). The reaction mixture was stirred at room temperature for 4 h. All volatiles were evaporated in vacuum and saturated  $\text{NH}_4\text{Cl}$  solution (20 mL) was added. The mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$ . Purification by column chromatography ( $\text{SiO}_2$ ,  $d \times h$ :  $2 \times 10$  cm, pentane: $\text{Et}_2\text{O}$  (10:1)) afforded the product (782 mg, 3.42 mmol, 50%) as a colorless solid.

$\text{C}_{14}\text{H}_{13}\text{NO}_2$  (227.26 g/mol):

**MP:** 31-32  $^\circ\text{C}$ .

**TLC:**  $R_f$  = 0.23 (pentane: $\text{Et}_2\text{O}$  (1:10), UV).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.08 (d,  $^3J_{\text{HH}}$  = 8.5 Hz, 2H,  $\text{ar-H}$ ), 7.52 (d,  $^3J_{\text{HH}}$  = 8.5 Hz, 2H,  $\text{ar-H}$ ), 6.04 (ddt,  $J$  = 17.3, 10.4, 5.7 Hz, 1H,  $\text{CH}_2=\text{CHCH}_2$ ), 5.69 (q,  $^4J_{\text{HH}}$  = 1.1 Hz, 1H,  $\text{C}=\text{CH}$ ), 5.46-5.36 (m, 1H,  $\text{CH}_2=\text{CH}$ ), 5.33-5.25 (m, 1H,  $\text{CH}_2=\text{CH}$ ), 4.85-4.82 (m, 2H,  $\text{OCH}_2$ ), 2.49 (d,  $^4J_{\text{HH}}$  = 1.1 Hz, 3H,  $\text{CH}_3$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 165.6 (s,  $\text{C}=\text{O}$ ), 158.9 (s,  $\text{C}=\text{CH}$ ), 142.7 (s,  $\text{ar-}q\text{C}$ ), 132.2 (s,  $\text{CH}_2=\text{CH}$ ), 131.8 (s,  $\text{ar-}q\text{C}$ ), 130.3 (s,  $\text{ar-C}$ ), 126.1 (s,  $\text{ar-C}$ ), 118.8 (s,  $\text{CH}_2=\text{CH}$ ), 117.3 (s,  $\text{C}\equiv\text{N}$ ), 97.8 (s,  $\text{C}=\text{CH}$ ), 66.1 (s,  $\text{CH}_2$ ), 20.4 (s,  $\text{CH}_3$ ).

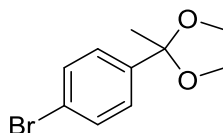
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3067 (w), 2961 (w), 2888 (w), 2211 (s), 1706 (s), 1606 (m), 1568 (w), 1459 (w), 1411 (m), 1362 (m), 1270 (s), 1186 (m), 1003 (m), 972 (m), 940 (s), 859 (m), 824 (m), 764 (s), 693 (m), 650 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 227.1 (11), 171.1 (33), 170.1 (100), 143.1 (22), 142.1 (22), 115.1 (20).

**EA** ( $\text{C}_{14}\text{H}_{13}\text{NO}_2$ ): calc.: C 73.99, H 5.77 N 6.16; found: C 74.28, H 5.78, N 6.33.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 28.24 min.

### 2-(4-Bromophenyl)-2-methyl-1,3-dioxolane (6.90)



To a solution of 4'-bromoacetophenone (8.50 g, 41.7 mmol, 1.00 eq.) in toluene (70 mL) ethylene glycol (3.88 mL, 3.48 g, 62.5 mol, 1.50 eq.) and *para*-toluenesulfonic acid monohydrate (396 mg, 2.08 mmol, 0.05 eq.) were added. A dean stark apparatus was attached and the solution was stirred for 16 h at reflux. The reaction mixture was washed with  $\text{NaHCO}_3$  (3  $\times$  30 mL), the organic layer was dried over  $\text{MgSO}_4$  and the solvent was evaporated under reduced pressure. Purification by bulb-to-bulb distillation (150 °C/0.1 bar) afforded the product (9.80 g, 40.3 mmol, 97%) as a colorless solid.

$\text{C}_{10}\text{H}_{11}\text{BrO}_2$  (243.10 g/mol):

**MP**: 43 °C.

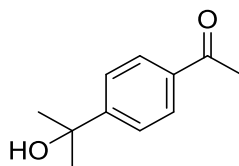
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.39-7.32 (m, 2H, ar-*H*), 7.28-7.23 (m, 2H, ar-*H*), 3.97-3.89 (m, 2H,  $\text{CH}_2$ ), 3.68-3.61 (m, 2H,  $\text{CH}_2$ ), 1.53 (s, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 142.6, 131.5, 127.3, 122.0, 108.6, 64.6, 27.7.

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 230.0 (10), 229.0 (97), 228.0 (10), 227.0 (100), 185.0 (44), 183.0 (47), 157.0 (10), 155.0 (11), 103.1 (11), 87.1 (32), 77.0 (11), 76.1 (13), 75.0 (12), 43.0 (73).

Obtained data are in accordance with literature data.<sup>[155]</sup>



**1-(4-(2-Hydroxypropan-2-yl)phenyl)ethan-1-one (6.91)**

Magnesia swarf (286 g, 11.8 mmol, 1.05 eq.) was layered with Et<sub>2</sub>O (5 mL) and 2-(4-bromophenyl)-2-methyl-1,3-dioxolane (146 mg, 0.56 mmol, 0.05 eq.) was added. After starting of the reaction a solution of 2-(4-bromophenyl)-2-methyl-1,3-dioxolane (2.58 g, 10.6 mmol, 0.95 eq.) in Et<sub>2</sub>O (35 mL) was added and the reaction mixture was stirred for 16 h at room temperature. H<sub>2</sub>O (30 mL) was added and the reaction mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the solvent was evaporated under reduced pressure. The crude acetal was dissolved in a dioxane:H<sub>2</sub>O mixture (1:1, 100 mL), 3 M HCl (25 mL) was added and the mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL) and the combined organic layers were dried over MgSO<sub>4</sub>. Purification by column chromatography (SiO<sub>2</sub>, d × h: 3 × 20 cm, cyclohexane:EtOAc (2:1)) afforded the product (1.78 g, 9.99 mol, 89%) as a colorless solid.

C<sub>11</sub>H<sub>14</sub>O<sub>2</sub> (178.23 g/mol):

**MP:** 78-80 °C.

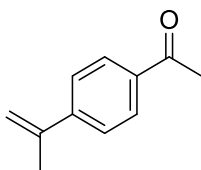
**TLC:** R<sub>f</sub> = 0.21 (SiO<sub>2</sub>, cyclohexane:ethyl acetate (5:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.90 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H, ar-*H*), 7.57 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H, ar-*H*), 2.57 (s, 3H, CH<sub>3</sub>), 2.20 (s, 1H, OH), 1.58 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 198.2 (s, C=O), 154.8 (s, ar-<sub>q</sub>C), 135.8 (s, ar-<sub>q</sub>C), 128.6 (s, ar-C), 124.9 (s, ar-C), 72.7 (s, COH), 31.9 (s, CH<sub>3</sub>), 26.8 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 164.1 (10), 163.1 (88), 121.1 (22), 43 (100).

Obtained data are in accordance with literature data.<sup>[156]</sup>

**1-(4-(Prop-1-en-2-yl)phenyl)ethan-1-one (6.92)**

A round bottomed flask was charged with 1-(4-(2-hydroxypropan-2-yl)phenyl)ethan-1-one (1.39 g, 7.80 mmol, 1.00 eq.) and potassium disulfate (604 mg, 2.34 mmol, 0.30 eq.). The reaction mixture was stirred for 90 min at 190 °C. Purification by column chromatography (SiO<sub>2</sub>, d × h: 2 × 20 cm, pentane:Et<sub>2</sub>O (2:1)) afforded the product (1.11 g, 6.91 mmol, 89%) as a colorless solid.

C<sub>11</sub>H<sub>12</sub>O (160.22 g/mol):

**MP:** 51-52 °C.

**TLC:** R<sub>f</sub> = 0.73 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (9:1), UV).

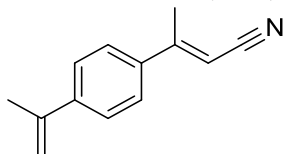
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.91 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H, ar-*H*), 7.53 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H, ar-*H*), 5.47 (s, 1H, C=CH<sub>2</sub>), 5.21-5.19 (m, 1H, C=CH<sub>2</sub>), 2.59 (s, 3H, CH<sub>3</sub>), 2.17 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 197.7 (s, C=O), 145.9 (s, ar-*q*C), 142.5 (s, C=CH<sub>2</sub>), 136.1 (s, ar-*q*C), 128.5 (s, ar-*C*), 125.7 (s, ar-*C*), 114.9 (s, C=CH<sub>2</sub>), 26.7 (s, CH<sub>3</sub>), 21.7 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3004 (w), 2977 (w), 2947 (w), 1915 (w), 1837 (w), 1669 (s), 1624 (w), 1602 (m), 1557 (m), 1463 (w), 1401 (m), 1356 (m), 1310 (w), 1268 (m), 1190 (m), 1120 (m), 1013 (m), 956 (m), 916 (m), 839 (s), 683 (w), 646 (m).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 160.1 (41), 146.1 (14), 145.1 (100), 117.1 (16), 115.1 (41), 91.1 (15).

Obtained data are in accordance with literature data.<sup>[157]</sup>

**(*E*)-3-(4-(Prop-1-en-2-yl)phenyl)but-2-enenitrile (6.94)**

The α,β-unsaturated nitrile was synthesized according to general procedure **GP9** using NaH (374 mg, 9.36 mmol, 1.50 eq., 60% in mineral oil) in THF (35 mL), diethyl

cyanomethylphosphonate (1.21 mL, 1.33 g, 7.49 mmol, 1.20 eq.), 1-(4-(prop-1-en-2-yl)phenyl)ethanone (1.00 g, 6.24 mmol, 1.00 eq.). Purification by column chromatography (SiO<sub>2</sub>, d × h: 5 × 24 cm, pentane:Et<sub>2</sub>O (45:1)) afforded the product (910 mg, 4.97 mmol, 80%) as a colorless solid.

C<sub>13</sub>H<sub>13</sub>N (183.25 g/mol):

**MP:** 62-63 °C.

**TLC:** R<sub>f</sub> = 0.51 (SiO<sub>2</sub>, pentane:Et<sub>2</sub>O (30:1), UV).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.50 (d, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz, 2H, ar-*H*), 7.44 (d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, 2H, ar-*H*), 5.64 (q, <sup>4</sup>J<sub>HH</sub> = 1.2 Hz, 1H, C=CH), 5.44 (s, 1H, C=H<sub>2</sub>), 5.17 (m, <sup>4</sup>J<sub>HH</sub> = 1.5 Hz, 1H, C=H<sub>2</sub>), 2.47 (d, <sup>4</sup>J<sub>HH</sub> = 1.1 Hz, 3H, CH<sub>3</sub>), 2.16 (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 159.2 (s, C=CH), 143.2, 142.3, 137.1 (s, ar-*q*C), 126.0 (s, ar-*C*), 125.9 (s, ar-*C*), 117.8 (s, C≡N), 114.0 (s, C=CH<sub>2</sub>), 95.2 (s, C=CH), 21.7 (s, CH<sub>3</sub>), 20.1 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3064 (w), 2987 (w), 2944 (w), 2211 (s), 1917 (w), 1832 (w), 1593 (s), 1508 (w), 1440 (m), 1379 (m), 1257 (m), 1120 (w), 1010 (w), 914 (s), 810 (s), 753 (m).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 184.1 (14), 183.1 (100), 182.1 (18), 168.1 (43), 167.1 (20), 153.1 (11), 143.1 (27), 141.1 (15), 128.1 (11), 115.1 (22).

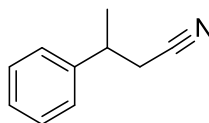
**EA** (C<sub>13</sub>H<sub>13</sub>N): calc.: C 85.21, H 7.15, N 7.64; found: C 84.94, H 7.14, N 7.71.

### 8.6.3 Hydrogenation products of $\alpha,\beta$ -unsaturated nitriles

#### General procedure: Iridium-catalyzed hydrogenation with DIPEA as additive GP10

Typical procedure for Ir-catalyzed hydrogenation with DIPEA as additive: The iridium catalyst (1.0 mol%) was added to a solution of substrate (0.10 mmol) and DIPEA (74.4  $\mu$ L, 0.45 mmol, 4.50 eq.) in MeOH (0.5 mL). The reaction vial was equipped with a magnetic stir bar and placed in an autoclave that was pressurized to 100 bar with H<sub>2</sub>. The reaction mixture was stirred at 800 rpm for 4 h and, after this time, hydrogen was released and the solvent removed under reduced pressure. The mixture was filtered through a plug of silica gel (d  $\times$  h: 0.5  $\times$  2.0 cm) using a mixture of pentane:Et<sub>2</sub>O (1:1, 5.0 mL). After evaporation of the solvent, the analytically pure hydrogenation product was obtained.

#### 3-Phenylbutanenitrile (6.17)



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

C<sub>10</sub>H<sub>11</sub>N (145.20 g/mol):

<sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ /ppm = 7.40-7.32 (m, 2H, ar-*H*), 7.30-7.23 (m, 3H, ar-*H*), 3.23-3.08 (m, 1H, CH), 2.68-2.50 (m, 2H, CH<sub>2</sub>), 1.42 (d, *J* = 7.0 Hz, 3H, CH<sub>3</sub>).

<sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ /ppm = 144.0 (s, ar-*qC*), 129.3 (s, ar-*C*), 127.7 (s, ar-*C*), 127.1 (s, ar-*C*), 119.1 (s, C $\equiv$ N), 37.1 (s, CH), 26.7 (s, CH<sub>2</sub>), 21.1 (s, CH<sub>3</sub>).

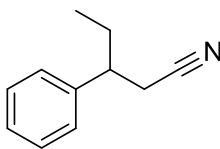
MS (EI, 70 eV, 200 °C) *m/z* (%): 145.1 (17), 105.1 (100), 130.1 (12), 79.1 (11), 77.1 (13).

GC (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): *t<sub>R</sub>* = 15.30 min.

HPLC: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min, 20 °C, 208 nm): *t<sub>R</sub>* = 32.0 min (–), 39.4 min (+).

Obtained data are in accordance with literature data.<sup>[110b]</sup>

### 3-Phenylpentanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{11}H_{13}N$  (159.23 g/mol):

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 7.40-7.29 (m, 2H, ar-*H*), 7.29-7.23 (m, 1H, ar-*H*), 7.22-7.13 (m, 2H, ar-*H*), 2.89-2.78 (m, 1H, CH), 2.60-2.56 (m, 2H,  $CH_2$ ), 1.96-1.83 (m, 1H,  $CH_2$ ), 1.80-1.61 (m, 1H,  $CH_2$ ), 0.84 (t,  $^3J_{HH}$  = 7.4 Hz, 3H,  $CH_3$ ).

$^{13}C\{^1H\}$  NMR (101 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 141.7 (s, ar- $qC$ ), 128.9 (s, ar- $C$ ), 127.4 (s, ar- $C$ ), 127.3 (s, ar- $C$ ), 118.8 (s,  $C\equiv N$ ), 43.9 (s, CH), 28.0 (s,  $CH_2$ ), 24.8 (s,  $CH_2$ ), 11.9 (s,  $CH_3$ ).

MS (EI, 70 eV, 200 °C)  $m/z$  (%): 159.1 (24), 130.1 (26), 119.1 (50), 103.1 (18), 91.1 (100), 77.1 (14).

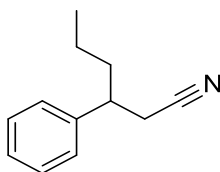
GC (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu m$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 16.74 min.

HPLC: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 215 nm):  $t_R$  = 19.6 min (–), 25.2 min (+).

$[\alpha]_D^{20} = -17.9$  ( $c$  = 0.90,  $CHCl_3$ ) for  $ee$  = 98%.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

### 3-Phenylhexanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{12}H_{15}N$  (173.26 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.38-7.33 (m, 2H, ar-*H*), 7.31-7.25 (m, 1H, ar-*H*), 7.25-7.19 (m, 2H, ar-*H*), 3.00-2.93 (m, 1H, CH), 2.60 (d,  $J$  = 6.9 Hz, 2H,  $\text{CH}_2$ ), 1.90-1.67 (m, 2H,  $\text{CH}_2$ ), 1.34-1.16 (m, 2H,  $\text{CH}_2$ ), 0.91 (t,  $J$  = 7.3 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 142.1 (s, ar- $\text{qC}$ ), 129.1 (s, ar- $\text{C}$ ), 127.5 (s, ar- $\text{C}$ ), 127.4 (s, ar- $\text{C}$ ), 118.9 (s,  $\text{C}\equiv\text{N}$ ), 42.2 (s, CH), 37.3 (s,  $\text{CH}_2$ ), 25.3 (s,  $\text{CH}_2$ ), 20.6 (s,  $\text{CH}_2$ ), 14.0 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3030 (w), 2959 (m), 2931 (m), 2872 (w), 2246 (w), 1603 (w), 1494 (w), 1454 (m), 1380 (m), 1331 (w), 1108 (w), 1073 (w), 1030 (w), 761 (m), 701 (s), 666 (m), 627 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 173.1 (14), 133.1 (27), 130.1 (16), 104.1 (13), 103.1 (12), 92.1 (10), 91.1 (100).

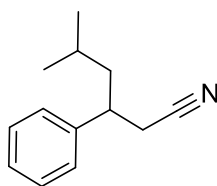
**HRMS** (EI): ( $m/z$ ) calc. for  $\text{C}_{12}\text{H}_{15}\text{N}^+$ : 173.1199  $[\text{M}]^+$ ; found: 173.1198.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_{\text{R}}$  = 18.26 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 98:02, 0.5 mL/min, 25 °C, 215 nm):  $t_{\text{R}}$  = 25.3 min (–), 33.7 min (+).

$[\alpha]_{\text{D}}^{20}$  = –13.9 ( $c$  = 1.2  $\text{CHCl}_3$ ) for  $ee$  = 98%.

### 5-Methyl-3-phenylhexanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$\text{C}_{13}\text{H}_{17}\text{N}$  (187.29 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.38-7.32 (m, 2H, ar-*H*), 7.30-7.20 (m, 3H, ar-*H*), 3.10-2.98 (m, 1H, CH), 2.56 (d,  $J$  = 6.9 Hz, 2H,  $\text{CH}_2$ ), 1.79-1.71 (m, 1H,  $\text{CH}_2$ ), 1.67-1.51 (m, 1H,  $\text{CH}_2$ ), 1.47-1.32 (m, 1H,  $\text{CH}(\text{CH}_3)$ ), 0.89 (m, 6H,  $\text{CH}(\text{CH}_3)_2$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 141.9 (s, ar- $q\text{C}$ ), 129.0 (s, ar- $\text{C}$ ), 127.4 (s, ar- $\text{C}$ ), 127.3 (s, ar- $\text{C}$ ), 118.7 (s,  $\text{C}\equiv\text{N}$ ), 44.1 (s,  $\text{CH}_2$ ), 40.1 (s,  $\text{CH}$ ), 25.7 (s,  $\text{CH}_2$ ), 25.4 (s,  $\text{CH}$ ), 23.3 (s,  $\text{CH}_3$ ), 21.7 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2957 (m), 2928 (w), 2870 (w), 14945 (w), 1468 (w), 1368 (w), 892 (w), 761 (w), 702 (m), 632 (s).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 187.1 (18), 147.2 (23), 131.1 (11), 130.1 (19), 105.1 (45), 104.1 (48), 103.1 (14), 91.1 (100), 77 (11).

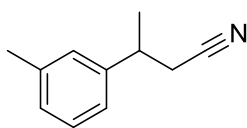
**HRMS** (EI): ( $m/z$ ) calc. for  $\text{C}_{13}\text{H}_{17}\text{N}^+$ : 187.1356  $[\text{M}]^+$ ; found: 187.1353.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_{\text{R}}$  = 18.96 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 212 nm):  $t_{\text{R}}$  = 19.7 min (–), 23.3 min (+).

$[\alpha]_{\text{D}}^{20}$  = +19.5 ( $c$  = 0.81,  $\text{CHCl}_3$ ) for  $ee$  = 98%.

### 3-(*m*-Tolyl)butanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$\text{C}_{11}\text{H}_{13}\text{N}$  (159.23 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.29-7.16 (m, 1H, ar- $H$ ), 7.13-6.97 (m, 3H, ar- $H$ ), 3.18-3.02 (m, 1H,  $\text{CH}$ ), 2.62-2.42 (m, 2H,  $\text{CH}_2$ ), 2.35 (d,  $^4J_{\text{HH}}$  = 0.9 Hz, 3H,  $\text{CH}_3$ ), 1.43 (d,  $^3J_{\text{HH}}$  = 7.0 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 143.2 (s, ar- $q\text{C}$ ), 138.5 (s, ar- $q\text{C}$ ), 128.1 (s, ar- $\text{C}$ ), 128.1 (s, ar- $\text{C}$ ), 127.4 (s, ar- $\text{C}$ ), 123.6 (s, ar- $\text{C}$ ), 118.7 (s,  $\text{C}\equiv\text{N}$ ), 36.6 (s,  $\text{CH}$ ), 26.4 (s,  $\text{CH}_2$ ), 21.5 (s,  $\text{CH}_3$ ), 20.8 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3025 (w), 2967 (w), 2924 (w), 2247 (w), 1608 (w), 1491 (m), 1458 (m), 1381 (m), 1345 (w), 1164 (w), 883 (w), 786 (m), 704 (s), 665 (m), 630 (s).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 159.1 (22), 120.1 (11), 119.1 (100), 117.1 (13), 91.1 (18).

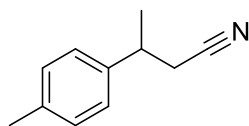
**HRMS** (EI): ( $m/z$ ) calc. for  $\text{C}_{11}\text{H}_{13}\text{N}^+$ : 159.1043  $[\text{M}]^+$ ; found: 159.1037.

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 16.86 min.

**HPLC**: *Daicel*, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 17.9 min (+), 21.2 min (–).

$[\alpha]_D^{20}$  = +0.3 (c = 1.06, CHCl<sub>3</sub>) for *ee* = 96%.

### 3-(*p*-Tolyl)butanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

C<sub>11</sub>H<sub>13</sub>N (159.23 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.23-7.02 (m, 4H, ar-*H*), 3.20-3.07 (m, 1H, *CH*), 2.60 (dd, <sup>2</sup>*J*<sub>HH</sub> = 16.7 Hz, <sup>3</sup>*J*<sub>HH</sub> = 6.5 Hz, 1H, *CH*<sub>2</sub>), 2.53 (dd, <sup>2</sup>*J*<sub>HH</sub> = 16.7 Hz, <sup>3</sup>*J*<sub>HH</sub> = 7.5 Hz, 1H, *CH*<sub>2</sub>), 2.35 (s, 3H, *CH*<sub>3</sub>), 1.44 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.0 Hz, 3H, *CH*<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 140.4 (s, ar-*qC*), 137.1 (s, ar-*qC*), 129.7 (s, ar-*C*), 126.6 (s, ar-*C*), 118.9 (s, *C*≡N), 36.3 (s, *CH*), 26.6 (s, *CH*<sub>2</sub>), 21.2 (s, *CH*<sub>3</sub>), 20.9 (s, *CH*<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 159.1 (17), 120.1 (10), 119.1 (100), 117.1 (13), 91.1 (18).

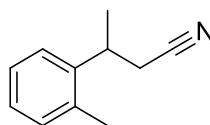
**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 17.10 min.

**HPLC**: *Daicel*, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 208 nm):  $t_R$  = 19.6 min (*S*), 23.0 min (*R*).

$[\alpha]_D^{20}$  = –2.0 (c = 0.61, CHCl<sub>3</sub>) for *ee* = 92% (*R*).

Obtained data are in accordance with literature data.<sup>[110b]</sup>



**3-(*o*-Tolyl)butanenitrile**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

C<sub>11</sub>H<sub>13</sub>N (159.23 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.25-7.02 (m, 4H, ar-*H*), 3.52-3.35 (m, 1H, CH), 2.66-2.44 (m, 2H, CH<sub>2</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 1.44 (d, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 3H, CH<sub>3</sub>).

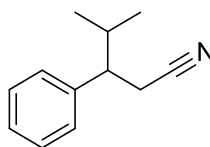
**<sup>13</sup>C{<sup>1</sup>H}NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 141.4 (s, ar-*qC*), 135.2 (s, ar-*C*), 130.9 (s, ar-*qC*), 127.1 (s, ar-*C*), 126.8 (s, ar-*C*), 124.8 (s, ar-*C*), 118.8 (s, C≡N), 31.8 (s, CH), 25.4 (s, CH<sub>2</sub>), 20.5 (s, CH<sub>3</sub>), 19.5 (s, CH<sub>3</sub>).

**MS** (EI, 70 eV, 200 °C) *m/z* (%): 159.1 (29), 119.1 (100), 117.1 (15), 91.1 (19).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): *t<sub>R</sub>* = 17.26 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 92:08, 0.5 mL/min, 25 °C, 208 nm): *t<sub>R</sub>* = 18.5 min, 31.0 min.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

**4-Methyl-3-phenylpentanenitrile**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

C<sub>12</sub>H<sub>15</sub>N (173.26 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.40-7.30 (m, 2H, ar-*H*), 7.30-7.23 (m, 1H, ar-*H*), 7.20-7.18 (m, 2H, ar-*H*), 2.76-2.55 (m, 3H, CH<sub>2</sub> and CH), 2.16-1.97 (m, 1H, CH), 1.02 (d, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz, 3H, CH<sub>3</sub>), 0.77 (d, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz, 3H, CH<sub>3</sub>).

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 141.3 (s, ar- $q\text{C}$ ), 128.8 (s, ar- $\text{C}$ ), 128.0 (s, ar- $\text{C}$ ), 127.4 (s, ar- $\text{C}$ ), 119.1 (s,  $\text{C}\equiv\text{N}$ ), 49.3 (s,  $\text{CH}$ ), 32.2 (s,  $\text{CH}$ ), 22.6 (s,  $\text{CH}_2$ ), 20.9 (s,  $\text{CH}_3$ ), 20.5 (s,  $\text{CH}_3$ ).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 173.1 (23), 133.2 (12), 131.1 (18), 130.1 (21), 105.1 (17), 104.2 (100), 103.1 (16), 91.1 (32), 77.1 (11).

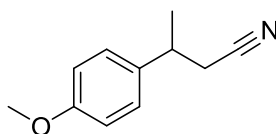
**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): 18.00 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 208 nm)  $t_R$  = 17.7 min (–), 27.8 min (+).

$[\alpha]_D^{20}$  = –12.6 ( $c$  = 0.96,  $\text{CHCl}_3$ ) for  $ee$  = 62%.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

### 3-(4-Methoxyphenyl)butanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$\text{C}_{11}\text{H}_{13}\text{NO}$  (175.23 g/mol):

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.17 (d,  $J$  = 8.7 Hz, 2H, ar- $H$ ), 6.88 (d,  $J$  = 8.7 Hz, 2H, ar- $H$ ), 3.80 (s, 3H,  $\text{OCH}_3$ ), 3.17–3.07 (m, 1H,  $\text{CH}$ ), 2.61–2.47 (m, 2H,  $\text{CH}_2$ ), 1.43 (d,  $J$  = 7.0 Hz, 3H,  $\text{CH}_3$ ).

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 158.9 (s, ar- $q\text{C}$ ), 135.4 (s, ar- $q\text{C}$ ), 127.7 (s, ar- $\text{C}$ ), 118.9 (s, ar- $\text{C}$ ), 114.4 (s,  $\text{C}\equiv\text{N}$ ), 55.4 (s,  $\text{OCH}_3$ ), 35.9 (s,  $\text{CH}$ ), 26.8 (s,  $\text{CH}_2$ ), 21.0 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2965 (m), 2935 (w), 2838 (w), 2246 (w), 1613 (m), 1584 (w), 1515 (s), 1460 (m), 1424 (w), 1298 (m), 1250 (s), 1181 (m), 1350 (m), 831 (m), 633 (s).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 175.1 (15), 136.1 (11), 135.1 (100), 105.1 (16).

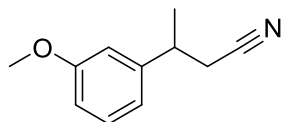
**EA** ( $\text{C}_{11}\text{H}_{13}\text{NO}$ ): calc.: C 75.40, H 7.48, N 7.99; found: C 75.11, H 7.39, N 7.95.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 22.45 min.

**HPLC:** *Daicel*, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 25 °C, 208 nm):  $t_R$  = 24.1 min (+), 28.2 min (–).

$[\alpha]_D^{20}$  = +9.6 ( $c$  = 0.96, CHCl<sub>3</sub>) for  $ee$  = 92%.

### 3-(3-Methoxyphenyl)butanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

C<sub>11</sub>H<sub>13</sub>NO (175.23 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.29-7.25 (m, 1H, ar-*H*), 6.85-6.76 (m, 3H, ar-*H*), 3.81 (s, 3H, OCH<sub>3</sub>), 3.13 (m, 1H, CH), 2.66-2.46 (m, 2H, CH<sub>2</sub>), 1.44 (d, <sup>3</sup> $J_{HH}$  = 7.0 Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 160.0 (s, ar-*qC*), 144.9 (s, ar-*qC*), 130.0 (s, ar-*C*), 118.9 (s, ar-*C*), 118.7 (s, C≡N), 112.8 (s, ar-*C*), 112.4 (s, ar-*C*), 55.3 (s, OCH<sub>3</sub>), 36.7 (s, CH), 26.3 (s, CH<sub>2</sub>), 20.7 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 2966 (s), 2939 (m), 2837 (m), 2247 (w), 1602 (s), 1571 (s), 1489 (s), 1455 (m), 1381 (w), 1347 (w), 1318 (w), 1294 (m), 1262 (s), 1160 (m), 1045 (m), 880 (m), 787 (w), 701 (m), 633 (s).

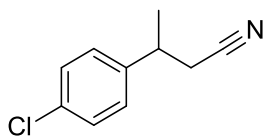
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 175.1 (28), 136.1 (11), 135.1 (100), 105.1 (20), 103.5 (10).

**HRMS** (EI): ( $m/z$ ) calc. for C<sub>11</sub>H<sub>13</sub>NO<sup>+</sup>: 175.0992 [M]<sup>+</sup>; found: 175.0990.

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 20.18 min.

**HPLC:** *Daicel*, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 92:08, 0.5 mL/min, 25 °C, 217 nm):  $t_R$  = 38.0 min (+), 56.2 min (–). (Due to overlay with starting material full conversion is necessary to determine the  $ee$  of this hydrogenation).

$[\alpha]_D^{20}$  = +1.5 ( $c$  = 0.92, CHCl<sub>3</sub>) for  $ee$  = 97%.

**3-(4-Chlorophenyl)butanenitrile**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP10** by the use of Crabtree's catalyst.

C<sub>10</sub>H<sub>10</sub>ClN (179.65 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.36-7.28 (m, 2H, ar-*H*), 7.22-7.11 (m, 2H, ar-*H*), 3.23-3.05 (m, 1H, *CH*), 2.68-2.40 (m, 2H, *CH*<sub>2</sub>), 1.43 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.0 Hz, 3H, *CH*<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 141.6 (s, ar-*qC*), 133.2 (s, ar-*qC*), 129.1 (s, ar-*C*), 128.1 (s, ar-*C*), 118.3 (s, *C*≡N), 36.1 (s, *CH*), 26.4 (s, *CH*<sub>2</sub>), 20.7 (s, *CH*<sub>3</sub>).

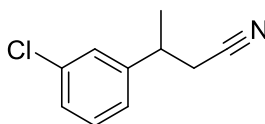
**MS** (EI, 70 eV, 200 °C) *m/z* (%): 179.1 (14), 141.1 (31), 139.1 (100), 103.1 (45), 77.1 (16).

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): *t*<sub>R</sub> = 20.04 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 220 nm): *t*<sub>R</sub> = 24.8 min (+), 27.1 min (–).

[α]<sub>D</sub><sup>20</sup> = –3.9 (c = 0.49, CHCl<sub>3</sub>) for *ee* = 97%.

Obtained data are in accordance with literature data.<sup>[110b]</sup>

**3-(3-Chlorophenyl)butanenitrile**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to to general procedure **GP10** by the use of Crabtree's catalyst.

C<sub>10</sub>H<sub>10</sub>ClN (179.65 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.31-7.19 (m, 3H, ar-*H*), 7.15-7.12 (m, 1H, ar-*H*), 3.13-3.10 (m, 1H, *CH*), 2.66-2.47 (m, 2H, *CH*<sub>2</sub>), 1.44 (d, *J* = 7.0 Hz, 3H, *CH*<sub>3</sub>).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 145.2 (s, ar- $q\text{C}$ ), 134.8 (s, ar- $q\text{C}$ ), 130.3 (s, ar- $\text{C}$ ), 127.7 (s, ar- $\text{C}$ ), 127.0 (s, ar- $\text{C}$ ), 125.0 (s, ar- $\text{C}$ ), 118.3 (s,  $\text{C}\equiv\text{N}$ ), 36.5 (s,  $\text{CH}$ ), 26.3 (s,  $\text{CH}_2$ ), 20.7 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3068 (w), 2970 (m), 2933 (w), 2249 (w), 1597 (m), 1273 (m), 1478 (m), 1432 (m), 1382 (w), 1341 (w), 1198 (w), 1084 (m), 882 (w), 698 (s), 632 (s).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 179.1 (21), 141.1 (31), 140.1 (10), 139.1 (100), 103.1 (44), 77.0 (14).

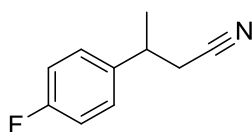
**HRMS** (EI): ( $m/z$ ) calc. for  $\text{C}_{10}\text{H}_{10}\text{ClN}^+$ : 179.0497  $[\text{M}]^+$ ; found: 179.0499.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_{\text{R}}$  = 19.85 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 220 nm):  $t_{\text{R}}$  = 27.7 min (+), 36.9 min (–).

$[\alpha]_{\text{D}}^{20}$  = +1.7 ( $c$  = 1.09,  $\text{CHCl}_3$ ) for  $ee$  = 97%.

### 3-(4-Fluorophenyl)butanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$\text{C}_{10}\text{H}_{10}\text{FN}$  (163.20 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.25-7.17 (m, 2H, ar- $H$ ), 7.08-6.99 (m, 2H, ar- $H$ ), 3.20-3.12 (m, 1H,  $\text{CH}$ ), 2.63-2.49 (m, 2H,  $\text{CH}_2$ ), 1.43 (d,  $^3J_{\text{HH}}$  = 7.0 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 162.1 (d,  $^1J_{\text{CF}}$  = 246 Hz, ar- $q\text{C}$ ), 139.0 (d,  $^4J_{\text{CF}}$  = 3 Hz, ar- $q\text{C}$ ), 128.3 (d,  $^3J_{\text{CF}}$  = 8 Hz, ar- $\text{C}$ ), 118.5 (s,  $\text{C}\equiv\text{N}$ ), 115.9 (d,  $^2J_{\text{CF}}$  = 21 Hz, ar- $\text{C}$ ), 36.0 (s,  $\text{CH}$ ), 26.7 (s,  $\text{CH}_2$ ), 20.9 (s,  $\text{CH}_3$ ).

**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = –115.1 (s).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3044 (w), 2970 (w), 2248 (w), 1605 (m), 1511 (s), 1459 (m), 1422 (m), 1383 (w), 1343 (w), 1224 (s), 1161 (m), 1094 (w), 1015 (m), 833 (s), 670 (m), 627 (m).

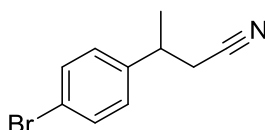
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 163.1 (14), 123.1 (100), 103.5 (36).

**HRMS** (EI): ( $m/z$ ) calc. for  $\text{C}_{10}\text{H}_{10}\text{FN}^+$ : 163.0792  $[\text{M}]^+$ ; found: 163.0793.

**GC** (*Chiraldex*  $\gamma$ -cyclodextrin TFA G-TA (30 m  $\times$  0.25 mm  $\times$  0.12  $\mu$ m), 60 kPa H<sub>2</sub> (50 °C – 0 min – 10 °C/min – 100 °C – 0 min – 2 °C/min – 140 °C – 10 °C/min – 160 °C – 5 min),  $t_R$  = 19.47 min (+), 19.87 min (–).

$[\alpha]_D^{20} = +0.5$  ( $c = 0.46$ , CHCl<sub>3</sub>) for  $ee = 90\%$ .

### 3-(4-Bromophenyl)butanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP10** by the use of Crabtree's catalyst.

C<sub>10</sub>H<sub>10</sub>BrN (224.10 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.47 (d,  $^3J_{HH} = 8.4$  Hz, 2H, ar-*H*), 7.13 (d,  $^3J_{HH} = 8.4$  Hz, 2H, ar-*H*), 3.20-3.05 (m, 1H, CH), 2.65-2.48 (m, 2H, CH<sub>2</sub>), 1.43 (d,  $^3J_{HH} = 7.1$  Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 142.2 (s, ar-*qC*), 132.1 (s, ar-*C*), 128.5 (s, ar-*C*), 121.3 (s, ar-*qC*), 118.3 (s, C $\equiv$ N), 36.2 (s, CH), 26.4 (s, CH<sub>2</sub>), 20.7 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}$ /cm<sup>-1</sup> = 2969 (m), 2929 (w), 2247 (m), 1901 (w), 1593 (w), 1489 (s), 1422 (m), 1334 (w), 1010 (s), 902 (w), 822 (s), 629 (w).

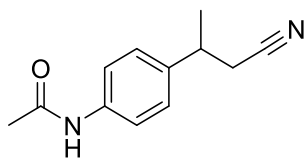
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 225.0 (24), 223.0 (24), 185.0 (88), 183.0 (88), 105.1 (10), 104.1 (100), 103.1 (23), 102.1 (11), 78.1 (11), 77.1 (19), 51.1 (10).

**HRMS** (EI): ( $m/z$ ) calc. for C<sub>10</sub>H<sub>10</sub>BrN<sup>+</sup>: 222.9992 [M]<sup>+</sup>; found: 222.9990.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 21.98 min.

**HPLC**: *Daicel*, Chiralpak AS-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 97:03, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 29.8 min (–), 34.3 min (+).

$[\alpha]_D^{20} = +2.8$  ( $c = 1.55$ , CHCl<sub>3</sub>) for  $ee = 97\%$ .

***N*-(4-(1-Cyanopropan-2-yl)phenyl)acetamide**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. MeOH was used as eluent. The racemic sample was prepared according to general procedure **GP8**.

C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O (143.19 g/mol):

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 7.47 (d, *J* = 8.5 Hz, 2H, ar-*H*), 7.39 (s br, 1H, NH), 7.19 (d, *J* = 8.5 Hz, 2H, ar-*H*), 3.20-3.06 (m, 1H, CH), 2.66-2.42 (m, 2H, CH<sub>2</sub>), 2.16 (s, 3H, CH<sub>3</sub>), 1.42 (d, *J* = 7.0 Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>): δ/ppm = 168.5 (s, C=O), 139.1 (s, ar-*qC*), 137.2 (s, ar-*qC*), 127.3 (s, ar-*C*), 120.5 (s, ar-*C*), 118.7 (s, C≡N), 36.1 (s, CH), 26.6 (s, CH<sub>2</sub>), 24.7 (s, CH<sub>3</sub>), 20.8 (s, CH<sub>3</sub>).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3310 (m), 3191 (w), 3123 (w), 3062 (w), 2967 (w), 1665 (s), 1601 (s), 1522 (s), 1458 (w), 1414 (s), 1371 (m), 1317 (s), 1363 (m), 1014 (m), 965 (w), 833 (m), 631 (s).

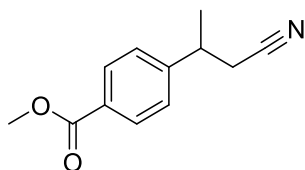
**MS** (EI, 70 eV, 200 °C) *m/z* (%): 202.1 (18), 162.1 (33), 121.1 (12), 120.1 (100), 43.0 (13).

**HRMS** (EI): (*m/z*) calc. for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sup>+</sup>: 202.1101 [M]<sup>+</sup>; found: 202.1102.

**GC** (Optima 5 (30 m × 0.25 mm × 0.5 μm) 60 kPa He (150 °C – 0 min – 10 °C/min – 250 °C – 20 min)): *t<sub>R</sub>* = 18.87 min.

**HPLC**: Daicel, Chiralpak IC (0.46 cm × 25 cm, heptane/iso-propanol = 80:20, 0.5 mL/min, 25 °C, 246 nm): *t<sub>R</sub>* = 61.0 min (–), 66.3 min (+).

$[\alpha]_D^{20}$  = +6.4 (*c* = 0.59, CHCl<sub>3</sub>) for *ee* = 96%.

**Methyl 4-(1-cyanopropan-2-yl)benzoate**

The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$\text{C}_{12}\text{H}_{13}\text{NO}_2$  (203.24 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.00 (d,  $^3J_{\text{HH}}$  = 8.3 Hz, 2H, ar-*H*), 7.31 (d,  $^3J_{\text{HH}}$  = 8.3 Hz, 2H, ar-*H*), 3.90 (s, 3H,  $\text{OCH}_3$ ), 3.26-3.17 (m, 1H, *CH*), 2.73-2.35 (m, 2H,  $\text{CH}_2$ ), 1.45 (d,  $^3J_{\text{HH}}$  = 7.0 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 166.9 (s,  $\text{C=O}$ ), 148.4 (s, ar- $q\text{C}$ ), 130.4 (s, ar-*C*), 129.5 (s, ar- $q\text{C}$ ), 126.9 (s, ar-*C*), 118.3 (s,  $\text{C}\equiv\text{N}$ ), 52.3 (s,  $\text{OCH}_3$ ), 36.7 (s, *CH*), 26.2 (s,  $\text{CH}_2$ ), 20.7 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 3067 (w), 2961 (w), 2888 (w), 2211 (s), 1706 (s), 1606 (m), 1568 (w), 1459 (w), 1411 (m), 1362 (m), 1270 (s), 1186 (m), 1003 (m), 972 (m), 940 (s), 859 (m), 824 (m), 764 (s), 693 (m), 650 (w).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 203.1 (20), 172.1 (20), 164.1 (12), 163.1 (100), 132.1 (15), 131.1 (17), 104.1 (13), 103.1 (14), 91.1 (13).

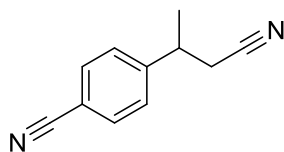
**HRMS** (EI): ( $m/z$ ) calc. for  $\text{C}_{12}\text{H}_{13}\text{NO}_2^+$ : 203.0941  $[\text{M}]^+$ ; found: 203.0944.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_{\text{R}}$  = 25.00 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 96:04, 0.5 mL/min, 25 °C, 233 nm):  $t_{\text{R}}$  = 42.3 min (+), 47.6 min (–).

$[\alpha]_{\text{D}}^{20}$  = –5.9 ( $c$  = 0.66,  $\text{CHCl}_3$ ) for  $ee$  = 98%.



**4-(1-Cyanopropan-2-yl)benzonitrile**

The enantiomerically enriched product was obtained as a colorless solid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{11}H_{10}N_2$  (170.22 g/mol):

**MP:** 47-48 °C.

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 7.66 (d,  $^3J_{HH}$  = 8.4 Hz, 2H, ar-*H*), 7.38 (d,  $^3J_{HH}$  = 8.3 Hz, 2H, ar-*H*), 3.22 (m, 1H, CH), 2.62-2.60 (m, 2H,  $CH_2$ ), 1.47 (d,  $^3J_{HH}$  = 7.0 Hz, 3H,  $CH_3$ ).

**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 148.4 (s, ar- $qC$ ), 132.9 (s, ar- $C$ ), 127.7 (s, ar- $C$ ), 118.7 (s,  $C\equiv N$ ), 117.8 (s,  $C\equiv N$ ), 111.7 (s, ar- $qC$ ), 36.8 (s, CH), 26.1 (s,  $CH_2$ ), 20.5 (s,  $CH_3$ ).

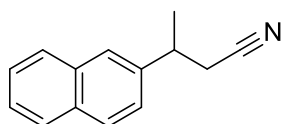
**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 170.1 (10), 131.1 (10), 130.1 (100), 103.1 (23).

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu m$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 25.53 min.

**HPLC:** Daicel, Chiralpak AS-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 60:40, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 18.7 min (–), 20.5 min (+).

$[\alpha]_D^{20}$  = +5.5 ( $c$  = 0.96,  $CHCl_3$ ) for  $ee$  = 93%.

Obtained data are in accordance with literature data.<sup>[158]</sup>

**3-(Naphthalen-2-yl)butanenitrile**

The enantiomerically enriched product was obtained as a colorless solid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{14}H_{13}N$  (195.26 g/mol):

**MP:** 54-57 °C.<sup>[66][63]</sup>

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 7.89-7.78 (m, 3H, ar-*H*), 7.71-7.67 (m, 1H, ar-*H*), 7.53-7.44 (m, 2H, ar-*H*), 7.37 (dd,  $^3J_{\text{HH}}$  = 8.5 Hz,  $^4J_{\text{HH}}$  = 1.9 Hz, 1H, ar-*H*), 3.38-3.30 (m, 1H, CH), 2.78-2.57 (m, 2H,  $\text{CH}_2$ ), 1.55 (d,  $^3J_{\text{HH}}$  = 7.0 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 140.6 (s, ar- $\text{qC}$ ), 133.6 (s, ar- $\text{qC}$ ), 132.8 (s, ar- $\text{qC}$ ), 128.8 (s, ar-*C*), 127.9 (s, ar-*C*), 127.8 (s, ar-*C*), 126.5 (s, ar-*C*), 126.1 (s, ar-*C*), 125.3 (s, ar-*C*), 124.9 (s, ar-*C*), 118.7 (s,  $\text{C}\equiv\text{N}$ ), 36.8 (s, CH), 26.4 (s,  $\text{CH}_2$ ), 20.9 (s,  $\text{CH}_3$ ).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 195.1 (23), 156.1 (13), 155.1 (100), 153.1 (16), 152.1 (10).

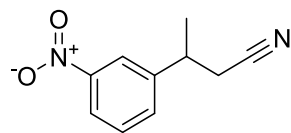
**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_{\text{R}}$  = 26.78 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 92:08, 0.5 mL/min, 25 °C, 276 nm):  $t_{\text{R}}$  = 34.9 min (+), 69.8 min (–).

$[\alpha]_{\text{D}}^{20}$  = +7.5 ( $c$  = 1.47,  $\text{CHCl}_3$ ) for  $ee$  = 98%.

Obtained data are in accordance with literature data.<sup>[159]</sup>

### 3-(3-Nitrophenyl)butanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP10** by the use of Crabtree's catalyst.

$\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$  (190.20 g/mol):

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 8.24-8.05 (m, 2H, ar-*H*), 7.66-7.59 (m, 1H, ar-*H*), 7.59-7.50 (m, 1H, ar-*H*), 3.38-3.24 (m, 1H, CH), 2.66 (dd,  $^3J_{\text{HH}}$  = 6.9 Hz,  $^4J_{\text{HH}}$  = 0.6 Hz, 2H,  $\text{CH}_2$ ), 1.51 (d,  $^3J_{\text{HH}}$  = 7.0 Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta/\text{ppm}$  = 148.7 (s, ar- $\text{qC}$ ), 145.1 (s, ar- $\text{qC}$ ), 133.2, (s, ar-*C*), 130.1 (s, ar-*C*), 122.7 (s, ar-*C*), 121.8 (s, ar-*C*), 117.9 (s,  $\text{C}\equiv\text{N}$ ), 36.5 (s, CH), 26.2 (s,  $\text{CH}_2$ ), 20.6 (s,  $\text{CH}_3$ ).

**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 2972 (w), 2932 (w), 2878 (w), 2250 (w), 1527 (s), 1459 (w), 1423 (w), 1349 (s), 1102 (w), 894 (w), 810 (w), 739 (m), 689 (m), 631 (m).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 190.1 (9), 150.1 (100), 120.1 (19), 104.1 (30), 103.1 (21), 78.0 (10), 77.1 (14).

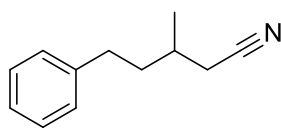
**HRMS** (EI): ( $m/z$ ) calc. for  $C_{13}H_{17}N_2O_2^+$ : 190.0737  $[M]^+$ ; found: 190.0733.

**GC-MS** (Restek Rtx-5MS (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 100 kPa He (50  $^{\circ}$ C – 2 min – 30  $^{\circ}$ C/min – 250  $^{\circ}$ C – 5 min):  $t_R$  = 8.96 min.

**HPLC**: Daicel, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 94:06, 0.5 mL/min, 25  $^{\circ}$ C, 220 nm):  $t_R$  = 51.6 min (–), 56.5 min (+).

$[\alpha]_D^{20}$  = –0.8 ( $c$  = 0.45,  $CHCl_3$ ) for  $ee$  = 93%.

### 3-Methyl-5-phenylpentanenitrile



The enantiomerically enriched product was obtained as a colorless liquid according to the standard hydrogenation protocol **GP10** using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{12}H_{15}N$  (173.26 g/mol):

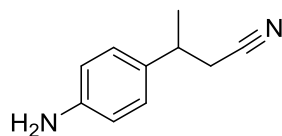
**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 7.33–7.24 (m, 2H, ar- $H$ ), 7.23–7.14 (m, 3H, ar- $H$ ), 2.69–2.60 (m, 2H, alkyl- $H$ ), 2.38–2.22 (m, 2H, alkyl- $H$ ), 1.88 (m, 1H, alkyl- $H$ ), 1.77 (ddt,  $J$  = 13.6, 9.5, 6.3 Hz, 1H, alkyl- $H$ ), 1.64 (m, 1H, alkyl- $H$ ), 1.13 (d,  $^3J_{HH}$  = 6.7 Hz, 3H,  $CH_3$ ).

**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$ /ppm = 141.6 (s, ar- $qC$ ), 128.6 (s, ar- $C$ ), 128.4 (s, ar- $C$ ), 126.2 (s, ar- $C$ ), 118.8 (s,  $C\equiv N$ ), 37.6 (s, alkyl- $C$ ), 33.2 (s, alkyl- $C$ ), 30.0 (s, alkyl- $C$ ), 24.6 (s, alkyl- $C$ ), 19.5 (s,  $CH_3$ ).

**MS** (EI, 70 eV, 200  $^{\circ}$ C)  $m/z$  (%): 173.2 (13), 158.2 (35), 92.1 (30), 91.1 (100), 65.1 (11).

**Chiral GC** ( $\beta$ -Cyclodextrin, DEtTButSil (Brebhühler, SE54), (25 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (50  $^{\circ}$ C – 0 min – 20  $^{\circ}$ C/min – 108  $^{\circ}$ C – 60 min – 5  $^{\circ}$ C/min – 180  $^{\circ}$ C – 5 min):  $t_R$  = 55.8 min (+), 56.3 min (–).

Obtained data are in accordance with literature data.<sup>[66]</sup>

**3-(4-Aminophenyl)butanenitrile**

The enantiomerically enriched product was obtained as a pale yellow solid according to the standard hydrogenation **GP10** protocol using iridium catalysts. The racemic sample was prepared according to general procedure **GP8**.

$C_{10}H_{12}N_2$  (160.22 g/mol):

**MP:** 38-40 °C.

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 7.03 (d,  $^3J_{HH}$  = 8.3 Hz, 2H, ar-*H*), 6.75-6.54 (m, 2H, ar-*H*), 3.63 (s, 2H,  $NH_2$ ), 3.10-3.01 (m, 1H, *CH*), 2.58-2.45 (m, 2H,  $CH_2$ ), 1.40 (d,  $^3J_{HH}$  = 7.0 Hz, 3H,  $CH_3$ ).

**$^{13}C\{^1H\}$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta/ppm$  = 145.7 (s, ar-*C*), 133.2 (s, ar-*C*), 127.5 (s, ar-*C*), 119.0 (s,  $C\equiv N$ ), 115.5 (s, ar-*C*), 35.9 (s, *CH*), 26.8 (s,  $CH_2$ ), 20.9 (s,  $CH_3$ ).

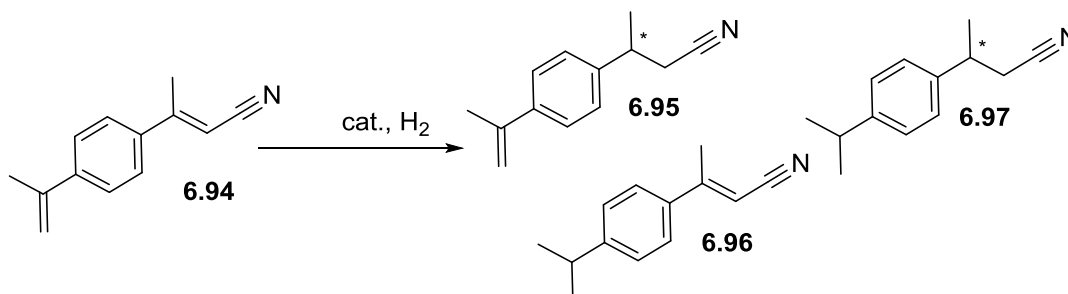
**IR** (ATR):  $\tilde{\nu}/cm^{-1}$  = 3463 (s), 3372 (s), 3219 (w), 3033 (w), 2960 (w), 2931 (w), 2248 (m), 1627 (s), 1518 (s), 1459 (m), 1440 (w), 1383 (w), 1294 (s), 1184 (m), 1130 (w), 1022 (w), 948 (w), 884 (w), 824 (s).

**MS** (EI, 70 eV, 200 °C)  $m/z$  (%): 160.1 (18), 121.1 (10), 120.1 (100).

**EA** ( $C_{10}H_{12}N_2$ ): calc.: C 74.97, H 7.55, N 17.48; found: C 74.95, H 7.51, N 17.67.

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu m$ ) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 23.13 min.

Analytical conditions for (*E*)-3-(4-(Prop-1-en-2-yl)phenyl)but-2-enenitrile.



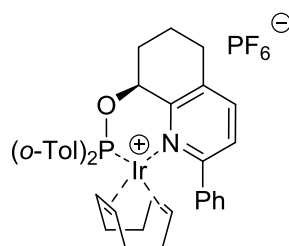
**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25 m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 21.37 min (**6.95**), 22.60 min (**6.94**), 19.59 min (**6.97**), 22.25 min (**6.96**).

**HPLC:** *Daicel*, Chiralcel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 95:5, 0.5 mL/min, 25 °C, 213 nm)  $t_R$  = 16.5 (**6.95**), 20.0 min (**6.95**), 14.1 min (**6.94**), 14.1 min (**6.97**), 14.6 min (**6.97**).

## 8.7 Recovery of iridium based catalysts for after the hydrogenation

### 8.7.1 Reisolation of catalysts and catalyst synthesis

**(R)-(-)-[1,5-Cycloocatdien-2-phenyl-8-(5,6,7,8-tetrahydrochinoliny)-di(2'-methylphenyl)-phosphinit-iridium(I)]-hexafluorophosphate (7.7)**



A pre-dried Schlenk flask was charged with (*R*)-2-phenyl-5,6,7,8-tetrahydroquinolin-8-ol (250 mg, 1.11 mmol, 1.00 eq.), 4-dimethylaminopyridine (163 mg, 1.33 mmol, 1.20 eq.) and chloro-di-(2-methylphenyl)phosphine (330 mg, 1.33 mmol, 1.20 eq.). The Schlenk flask was evacuated three times and each time backfilled with argon. The mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (7.5 mL) and stirred for 1 h at room temperature. A second preheated Schlenk flask was charged with [Ir(COD)Cl]<sub>2</sub> (410 mg, 0.611 mmol, 0.50 eq.) and assembled with a preheated Schlenk frit. The Schlenk frit was charged with basic aluminium oxide (d × h: 1 × 3 cm). The equipment was evacuated three times and each time backfilled with argon.

The ligand containing solution was filtered through the aluminium oxide layer and rinsed with CH<sub>2</sub>Cl<sub>2</sub> (4 × 5 mL). The new obtained reaction mixture was stirred for 2 h at room temperature. The solution was treated with NH<sub>4</sub>PF<sub>6</sub> (2 × 20 mL), washed with H<sub>2</sub>O (2 × 20 mL) and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure to afford a crude, red solid.

The crude was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and Et<sub>2</sub>O (17.5 mL) was added. The slightly turbid solution was filtrated and the filtrate cooled down to -24 °C and stored for 2 h at this temperature. Crystallization overnight afforded the product as red crystals (750 mg, 849 μmol, 77%).

C<sub>37</sub>H<sub>40</sub>F<sub>6</sub>IrNOP<sub>2</sub> (882.89 g/mol):

**MP:** 170-172 °C.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 7.82 (d,  $J$  = 8.1 Hz, 1H, ar-*H*), 7.77-7.66 (m, 3H, ar-*H*), 7.65-7.60 (m, 2H, ar-*H*), 7.59-7.51 (s, 1H, ar-*H*), 7.50 (1H, d,  $J$  = 8.1 Hz, ar-*H*), 7.46-7.40 (m, 2H, ar-*H*), 7.39-7.32 (m, 2H, ar-*H*), 7.30-7.22 (m, 1H, ar-*H*), 7.21-7.16 (m, 1H, ar-*H*), 6.89 (dd,  $J$  = 12.5, 7.9 Hz, 1H, ar-*H*), 6.31-6.24 (m, 1H, CHOP), 4.78-4.70 (m, 1H, CH(COD)), 4.51-4.42 (m, 1H, CH(COD)), 3.28-3.14 (s, 1H, CH(COD)), 3.08-3.00 (m, 1H,  $\text{CH}_2$ ), 2.98-2.86 (m, 4H,  $\text{CH}_3$ ,  $\text{CH}_2$ ), 2.85-2.78 (m, 1H, CH(COD)), 2.66-2.57 (m, 1H,  $\text{CH}_2$ ), 2.55-2.35 (m, 5H,  $\text{CH}_3$ ,  $\text{CH}_2$ ,  $\text{CH}_2(\text{COD})$ ), 2.14-1.96 (m, 3H,  $\text{CH}_2$ ,  $\text{CH}_2(\text{COD})$ ), 1.95-1.79 (m, 3H,  $\text{CH}_2(\text{COD})$ ), 1.42-1.30 (m, 1H,  $\text{CH}_2(\text{COD})$ ), 1.30-1.18 (m, 1H,  $\text{CH}_2(\text{COD})$ ), 1.15-1.04 (m, 1H,  $\text{CH}_2(\text{COD})$ ).

**$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 160.4 (s, ar-C), 154.4 (s, ar-C), 141.9 (d,  $J$  = 9.7 Hz, ar-C), 141.5 (s, ar-C), 139.5 (s, ar-C), 136.6 (s, ar-C), 134.8 (s, ar-C), 134.3 (s, ar-C), 132.8 (d,  $J$  = 8.0 Hz, ar-C), 132.6 (s, ar-C), 132.5 (d,  $J$  = 2.2 Hz, ar-C), 132.5 (s, ar-C), 132.4 (d,  $J$  = 1.9 Hz, ar-C), 131.9 (s, ar-C), 131.8 (s, ar-C), 131.7 (s, ar-C), 130.2 (s, ar-C), 128.1 (s, ar-C), 126.7 (d,  $J$  = 10.6 Hz, ar-C), 126.5 (d,  $J$  = 11.5 Hz, ar-C), 126.3 (s, ar-C), 95.0 (d,  $J$  = 7.5 Hz, CH(COD)), 83.0 (d,  $J$  = 20.5 Hz, CH(COD)), 76.7 (s, CH(COD)), 70.0 (s, CH(COD)), 69.8 (s, CHOP), 36.3 (d,  $J$  = 3.5 Hz,  $\text{CH}_2$ ), 35.0 (s,  $\text{CH}_2$ ), 30.9 (d,  $J$  = 9.8 Hz,  $\text{CH}_2$ ), 29.1 (s,  $\text{CH}_2$ ), 28.9 (s,  $\text{CH}_2$ ), 24.2 (s,  $\text{CH}_2$ ), 23.2 (d,  $J$  = 5.9 Hz,  $\text{CH}_3$ ), 22.4 (d,  $J$  = 5.5 Hz,  $\text{CH}_3$ ), 18.9 (s,  $\text{CH}_2$ ).

**$^{31}\text{P}\{^1\text{H}\}$  NMR** (162 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta/\text{ppm}$  = 98.1 (s), 144.5 (sept).

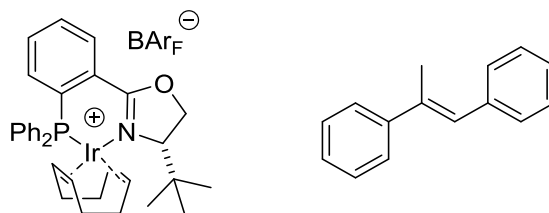
**IR** (ATR):  $\tilde{\nu}/\text{cm}^{-1}$  = 1466 (w), 1450 (w), 1206 (w), 1073 (w), 965 (w), 929 (w), 833 (s), 760 (m), 671 (w), 556 (s).

**HRMS** (ESI, 4500 V, 180 °C): ( $m/z$ ) calc. for  $\text{C}_{37}\text{H}_{40}\text{IrNOP}^+$ : 738.2485  $[\text{M}-\text{PF}_6]^+$ ; found: 738.2473.

**$[\alpha]_D^{20}$**  = +20.6 ( $c$  = 0.45,  $\text{CHCl}_3$ ).

**General procedure: Recovery [Ir(L)COD)]BAr<sub>F</sub> catalysts GP11**

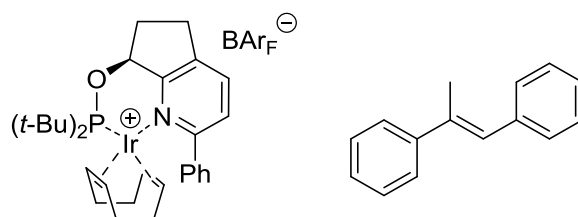
A glass inlet of an autoclave was charged with the respective iridium catalyst (1% mol) and the substrate dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.2 M) was added. The glass inlet was placed in an autoclave that was pressurized to 50 bar with H<sub>2</sub>. The reaction mixture was stirred for 2 h at 700 rpm. The autoclave was opened under normal atmosphere and the reaction mixture was transferred to a round bottom flask, which was previously purged with argon for 5 min. 1,5-Cyclooctadiene (0.10 eq.) was added and the reaction mixture was stirred for 1 h at room temperature. All volatiles were evaporated under reduced pressure. Purification of the residue by column chromatography (SiO<sub>2</sub>) afforded by the use of the first eluent mixture the hydrogenated substrate and by the second eluent mixture the catalyst.

**Recovery of diphenylphosphine *tert*-butyl PHOX catalyst 7.11**

The reaction was set up according to general procedure **GP11** using 30.4 mg catalyst and *trans*-methyl stilbene as substrate. Purification by column chromatography (SiO<sub>2</sub>, d × h: 2 × 5 cm, 1. pentane:Et<sub>2</sub>O (1:1, 100 mL), 2. CH<sub>2</sub>Cl<sub>2</sub> (30 mL)) afforded the complex (20.2 mg, 13 μmol, 66%) as a red solid.

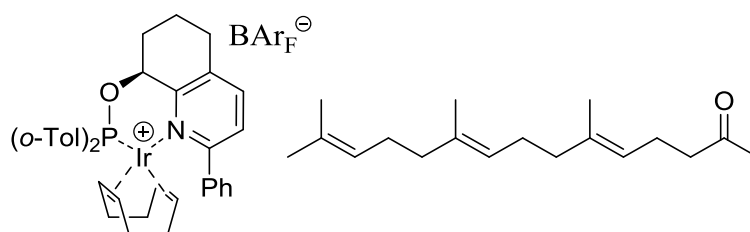
Analytical data of the substrate<sup>[160]</sup> are in accordance with literature data. The recovered catalyst matches the data of the applied catalyst.



**Recovery of pyridine based catalyst 7.10**

The reaction was set up according to general procedure **GP11** using 30.0 mg catalyst and *trans*-methyl stilbene as substrate. Purification by column chromatography (SiO<sub>2</sub>, d × h: 2 × 5 cm, 1. pentane:Et<sub>2</sub>O (100 mL), 2. CH<sub>2</sub>Cl<sub>2</sub> (40 mL)) afforded the complex (18.1 mg, 12 μmol, 60%) as an orange solid.

Analytical data of the substrate<sup>[160]</sup> and the recovered catalyst<sup>[52b]</sup> are in accordance with literature data.

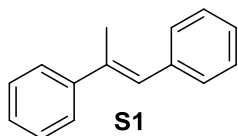
**Recovery of pyridine based catalyst 7.5**

The reaction was set up according to general procedure **GP11** using (40.0 mg, 25.0 μmol, 1.0 mol%) catalyst and (5*E*,9*E*)-farnesylacetone (656 mg, 2.50 mmol), in CH<sub>2</sub>Cl<sub>2</sub> (12.5 mL). Purification by column chromatography (SiO<sub>2</sub>, d × h: 2 × 10 cm) afforded the product (663 mg, 2.47 mmol, 99%) with (Pentan:Et<sub>2</sub>O, (1:1)) followed by eluting the catalyst (27.9 mg, 17.4 μmol, 70%) with CH<sub>2</sub>Cl<sub>2</sub>.

Analytical data of the substrate<sup>[161]</sup> and the recovered catalyst<sup>[52b]</sup> are in accordance with literature data.

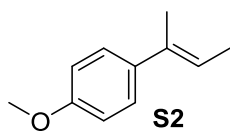
## 8.8 Analytical Data for the Model Substrates

### (*E*)-Prop-1-ene-1,2-diylidibenzene (**S1**)



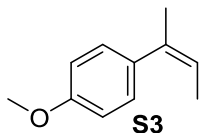
**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 18.3 min (**P1**), 21.4 min (**S1**). **HPLC**: *Daicel*, Chiracel OJ (0.46 cm × 25 cm, heptane/iso-propanol = 99:01, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 15.6 min ((*R*)-**S1**), 23.8 min ((*S*)-**S1**).

### (*E*)-2-(4-Methoxyphenyl)-2-butene (**S2**)



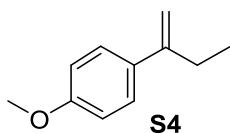
**GC** (*ChiralDEX* γ-cyclodextrin TFA G-TA (30 m × 0.25 mm × 0.12 μm), 60 kPa H<sub>2</sub> (60 °C – 30 min – 5 °C/min – 100 °C – 0 min – 10 °C/min – 160 °C – 10 ° min),  $t_R$  = 38.4 min ((*S*)-**P2**), 38.6 min ((*R*)-**P2**), 41.2 min (**S2**).

### (*Z*)-2-(4-Methoxyphenyl)-2-butene (**S3**)



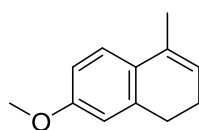
**GC** (*ChiralDEX* γ-cyclodextrin TFA G-TA (30 m × 0.25 mm × 0.12 μm), 60 kPa H<sub>2</sub> (60 °C – 30 min – 5 °C/min – 100 °C – 0 min – 10 °C/min – 160 °C – 10 ° min),  $t_R$  = 38.4 min ((*S*)-**P2**), 38.6 min ((*R*)-**P2**), 39.3 min (**S3**).

### 2-(4-Methoxyphenyl)-1-butene (**S4**)

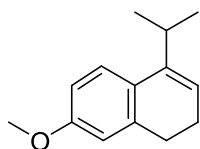


**GC** (*ChiralDEX* γ-cyclodextrin TFA G-TA (30 m × 0.25 mm × 0.12 μm), 60 kPa H<sub>2</sub> (60 °C – 30 min – 5 °C/min – 100 °C – 0 min – 10 °C/min – 160 °C – 10 ° min),  $t_R$  = 38.4 min ((*S*)-**P2**), 38.6 min ((*R*)-**P2**), 40.3 min (**S4**).

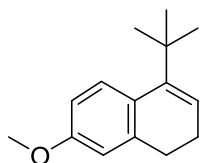
### 7-Methoxy-1,2-dihydro-naphthalene (**S5**)



**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 15.0 min (**P5**), 17.6 min (**S5**), 19.8 min (naphthalene derivative). **HPLC**: *Daicel*, Chiracel OD-H (0.46 cm × 25 cm, heptane, 0.75 mL/min, 25 °C, 220 nm):  $t_R$  = 20.4 min ((*R*)-**P5**), 27.0 min ((*S*)-**P5**).

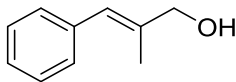
**4-Isopropyl-7-methoxy-1,2-dihydronaphthalene (S6)**

**GC** (chiral,  $\beta$ -Cyclodextrin, DEtTButSil (Brechtbühler, SE54 (25 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa H<sub>2</sub> (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 10.8 min ((*S*)-**P6a**),  $t_R$  = 11.3 min ((*R*)- **P6a**),  $t_R$  = 12.5 min (**S6**),  $t_R$  = 15.0 min (**P6b**).

**4-(*tert*-Butyl)-7-methoxy-1,2-dihydronaphthalene (S7)**

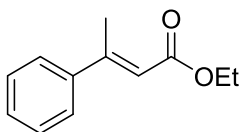
**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min): 20.82 min (**P7a**), 21.46 min (**S7**), 23.39 min (**P7b**)

**HPLC**: Daicel, Chiracel OD-H (0.46 cm  $\times$  25 cm, heptane, 1.00 mL/min, 25 °C, 220 nm):  $t_R$  = 6.4 min (**P7a**),  $t_R$  = 8.7 min (**P7a**),  $t_R$  = 14.7 min (**S7**),  $t_R$  = 10.8 min (**P7b**)

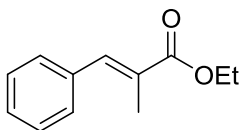
**(*E*)-2-Methyl-3-phenylprop-2-en-1-ol (S8)**

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 14.6 min (**P8**), 16.5 min (**S8**).

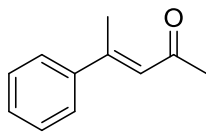
**HPLC**: Daicel, Chiracel OD-H (0.46 cm  $\times$  25 cm, heptane/iso-propanol = 95:05, 0.5 mL/min, 40 °C, 220 nm):  $t_R$  = 15.3 min ((*R*)-**P8**), 17.5 min ((*S*)-**P8**), 19.6 min (**S8**).

**(*E*)-Ethyl 3-phenylbut-2-enoate (S9)**

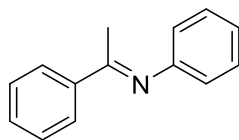
**GC** (ChiralDEX  $\gamma$ -cyclodextrin TFA G-TA (30 m  $\times$  0.25 mm  $\times$  0.12  $\mu$ m), 60 kPa H<sub>2</sub> (60 °C – 30 min – 5 °C/min – 100 °C – 0 min – 10 °C/min – 160 °C – 10 ° min),  $t_R$  = 42.9 min ((*R*)-**P9**), 44.9 min ((*S*)-**P9**), 57.0 min (**S9**).

**Ehyl (*E*)-2-methyl-3-phenylacrylate (S10)**

**GC** (Restek Rtx-1701 (30 m  $\times$  0.25 mm  $\times$  0.25  $\mu$ m) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 14.5 min (**P10**), 17.2 min (**S10**). **HPLC**: Daicel, Chiracel OB-H (0.46 cm  $\times$  25 cm, heptanes, 0.5 mL/min, 20 °C, 220 nm):  $t_R$  = 22.7 min ((*R*)-**P10**), 25.3min ((*S*)-**P10**).

**(E)-4-Phenylpent-3-en-2-one (S12)**

**GC** (Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) 60 kPa He (100 °C – 2 min – 7 °C/min – 250 °C – 10 min):  $t_R$  = 13.9 min (**P12**), 16.0 min (**S12**). **HPLC**: *Daicel*, Chiracel AS-H (0.46 cm × 25 cm, heptane/iso-propanol = 99.3:0.7, 0.5 mL/min, 20 °C, 220 nm):  $t_R$  = 20.5min ((*S*)-**P12**), 24.7min ((*R*)-**P12**).

**(E)-N-(1-phenylethylidene)aniline (S14)**

**GC** (Optima 5 (30 m × 0.25 mm × 0.5 μm) 60 kPa He (150 °C – 0 min – 7 °C/min – 250 °C – 10 min)):  $t_R$  = 12.6 min (**P14**), 12.9 min (**S14**), 4.9 min acetophenone, 5.4 min aniline. **HPLC**: *Daicel*, Chiracel OD-H (0.46 cm × 25 cm, heptane/iso-propanol = 99:01, 0.5 mL/min, 25 °C, 220 nm):  $t_R$  = 24.6 min ((*S*)-**P14**), 33.0 min ((*R*)-**P14**).

## 9 Appendix

### 9.1 Crystallographic data

Compound	2.83	( <i>R</i> )-2.63
formula	C <sub>74</sub> H <sub>52</sub> BCl <sub>2</sub> F <sub>24</sub> IrNOP	C <sub>72</sub> H <sub>74</sub> BF <sub>24</sub> IrNO <sub>2</sub> P
M <sub>r</sub> [g × mol <sup>-1</sup> ]	1732.09	1675.34
shape	plate	block
color	red	orange
space group	P-1	C 2
crystal size	0.02 × 0.15 × 0.18 mm <sup>3</sup>	0.09 × 0.19 × 0.23 mm <sup>3</sup>
<i>a</i> [Å]	15.8491(11)	44.280(2)
<i>b</i> [Å]	15.8906(11)	12.7293(6)
<i>c</i> [Å]	16.253(2)	25.6592(11)
α [°]	96.195(3)	90
β [°]	105.164(3)	95.409(4)
γ [°]	115.839(2)	90
V [Å <sup>3</sup> ]	3437.8(6)	14398.4(11)
Z	2	8
F(000)	1716	6736
Θ range of data detection [°]	3.196-68.417	1.665-30.522
ρ calc [g × cm <sup>-3</sup> ]	1.673	1.546
absorption coeff. μ [mm <sup>-1</sup> ]	5.697	1.984
measured reflections	47103	135833
independent reflections	12256 (merging <i>r</i> = 0.047)	42181 (merging <i>r</i> = 0.065)
used reflections	12256	28295
parameters refined	1020	1866
<i>R</i>	0.0351	0.0442
<i>R</i> <sub>w</sub>	0.0415	0.0667
Goodness of fit	1.0847	0.9750

Compound	(S)-2.77	(S)-2.72
formula	C <sub>69</sub> H <sub>52</sub> BF <sub>24</sub> IrNOP	C <sub>63</sub> H <sub>54</sub> B <sub>1</sub> F <sub>26</sub> IrNOP
M <sub>r</sub> [g × mol <sup>-1</sup> ]	1601.13	1569.08
shape	plate	needle
color	orange	orange
space group	P 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	P 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
crystal size	0.03 × 0.09 × 0.21 mm <sup>3</sup>	0.02 × 0.05 × 0.23 mm <sup>3</sup>
<i>a</i> [Å]	13.0563(3)	13.7895(7)
<i>b</i> [Å]	13.1861(3)	17.2803(8)
<i>c</i> [Å]	36.8217(8)	26.5684(13)
α [°]	90	90
β [°]	90	90
γ [°]	90	90
V [Å <sup>3</sup> ]	6339.3(2)	6330.9(5)
Z	4	4
F(000)	3176	3112
Θ range of data detection [°]	1.640-30.036	3.051-68.215
ρ calc [g × cm <sup>-3</sup> ]	1.678	1.646
absorption coeff. μ [mm <sup>-1</sup> ]	2.248	5.399
measured reflections	116807	52927
independent reflections	18534 (merging r = 0.050)	11246 (merging r = 0.038)
used reflections	16162	10454
parameters refined	884	959
<i>R</i>	0.0253	0.0249
<i>R</i> <sub>w</sub>	0.0259	0.0306
Goodness of fit	1.1083	1.1417

Compound	(S)-2.78
formula	C <sub>71</sub> H <sub>72</sub> BF <sub>24</sub> IrNO <sub>2</sub> P
M <sub>r</sub> [g × mol <sup>-1</sup> ]	1661.32
shape	block
color	orange
space group	P 1
crystal size	0.060 × 0.16 × 0.19 mm <sup>3</sup>
<i>a</i> [Å]	13.5575(7)
<i>b</i> [Å]	15.0582(8)
<i>c</i> [Å]	18.9181(9)
α [°]	90.286(2)
β [°]	90.286(2)
γ [°]	101.754(2)
V [Å <sup>3</sup> ]	3576.7(3)
Z	2
F(000)	1668.000
Θ range of data detection [°]	3.006-68.206
ρ calc [g × cm <sup>-3</sup> ]	1.542
absorption coeff. μ [mm <sup>-1</sup> ]	4.780
measured reflections	49427
independent reflections	22908 (merging r = 0.027)
used reflections <sup>[a]</sup>	21661
parameters refined	1968
<i>R</i>	0.0237
<i>R</i> <sub>w</sub>	0.0280
Goodness of fit	1.1035

## 9.2 List of Abbreviations

Å	Angstrom ( $1 \text{ Å} = 10^{-10} \text{ m}$ )
Ac	acetyl
Ant	anthracenyl
Ar	aryl
BAr <sub>F</sub>	tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BPPM	butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidin
br	broad
Bu	butyl
°C	Grad Celsius
<i>c</i>	concentration
CAL-B	<i>Candida Antartica</i> Lipase B
calc.	calculated
cat.	catalyst
COD	cycloocta-1,5-diene
conv.	conversion
COSY	correlation spectroscopy
Cy	cyclohexyl
d	day(s) or doublet (NMR)
D	sodium D line
d (NMR)	chemical shift
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	<i>N,N</i> -4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenyl-phosphino)ferrocene
<i>E</i>	opposite
EA	elemental analysis
<i>ee</i>	enantiomeric excess
EI	Electron-imp
eq.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
FAB	fast atom bombardement
GC	gas chromatography
h	hour(s)
hmbc	heteronuclear multiple bond coherence
<i>hmqc</i>	heteronuclear multiple bond coherence
HPLC	high performance liquid chromatography
Hz	Hertz
<i>i</i> -Pr	2-propyl
J	coupling constante



K	Kelvin
LDA	lithium diisopropylamide
M	molar [mol/L]
<i>m</i>	meta
m	multiplet (NMR) or medium (IR)
MP	melting point
<i>m/z</i>	mass-to-charge ratio
MALDI	matrix assisted laser desorption ionization
MCPBA	3-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
Mes	mesityl
min	minute(s)
mL	milliliter
MS	mass spectrometry or molecular sieves
<i>n</i>	normal
n.d.	not determined
n.o.	not observed
NBA	3-nitrobenzyl alcohol
nbd	norbornadiene
<i>n</i> -BuLi	1-butyl lithium
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
<i>o</i>	ortho
<i>o</i> -Tol	<i>ortho</i> -tolyl
<i>p</i>	para
Ph	phenyl
PHIM	phosphino-imidazoline
PHOX	phosphino-oxazoline
pin	pinacolborane
ppm	parts per million
q (NMR)	quartet
quint (NMR)	quintet
<i>rac.</i>	racemic
<i>R<sub>f</sub></i>	retention factor
RT	room temperature
s	singlet (NMR) or strong (IR)
sat.	saturated
sec	second(s)
T	time
t (NMR)	triplet
<i>t</i> or <i>tert</i>	tertiary
TBAI	tetrabutylammonium iodide
TBAF	tetrabutylammonium fluoride
TBME	<i>tert</i> -butyl methyl ether
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
<i>t</i> -BuLi	<i>tert</i> -butyl lithium
TEA	triethylamine
THF	tetrahydrofuran

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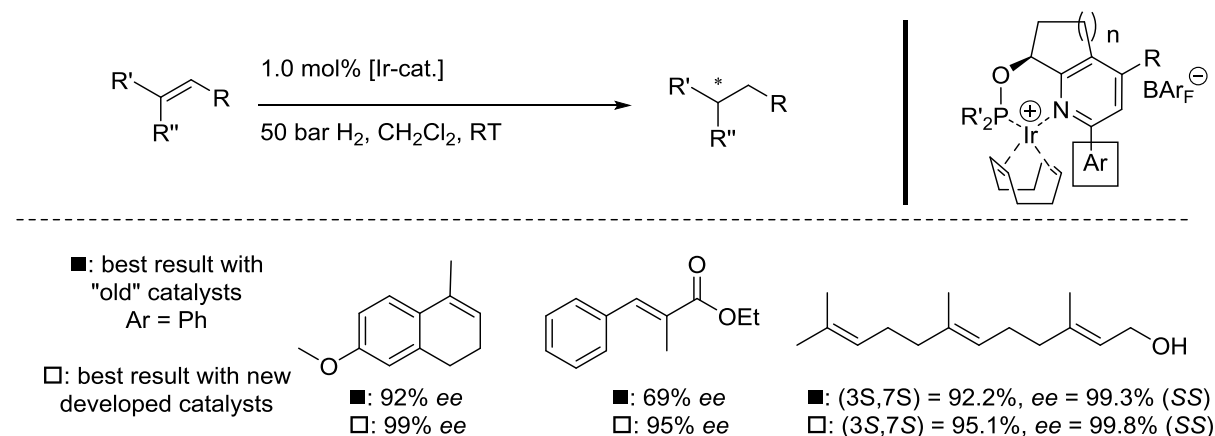
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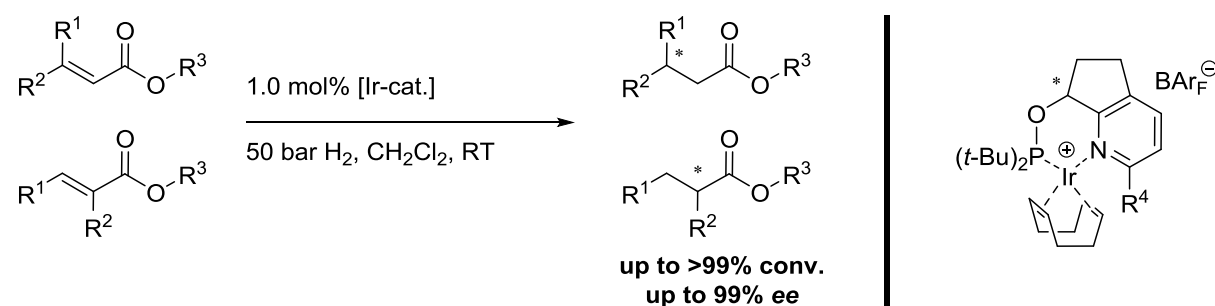
The objective of this thesis was the synthesis and further development of different iridium N,P ligand complexes as well as the evaluation and application of different challenging substrate classes in the asymmetric hydrogenation using iridium-based catalysts.

The first chapter of this thesis deals with the further development of bicyclic pyridine-based ligands. A late stage Suzuki–Miyaura cross-coupling allowed for the synthesis of a large variety of different ligands for which a phenyl group was exchanged with more sterically demanding aryl-group. Iridium complexes of these new ligands emerged as efficient catalysts for the asymmetric hydrogenation of different functionalized and unfunctionalized olefins. For several substrate classes superior results were achieved compared to the original catalysts (scheme 11.1).



**Scheme 11.1:** Bicyclic pyridine-based iridium complexes with sterically demanding aryl groups as efficient catalysts in the hydrogenation of different substrates.

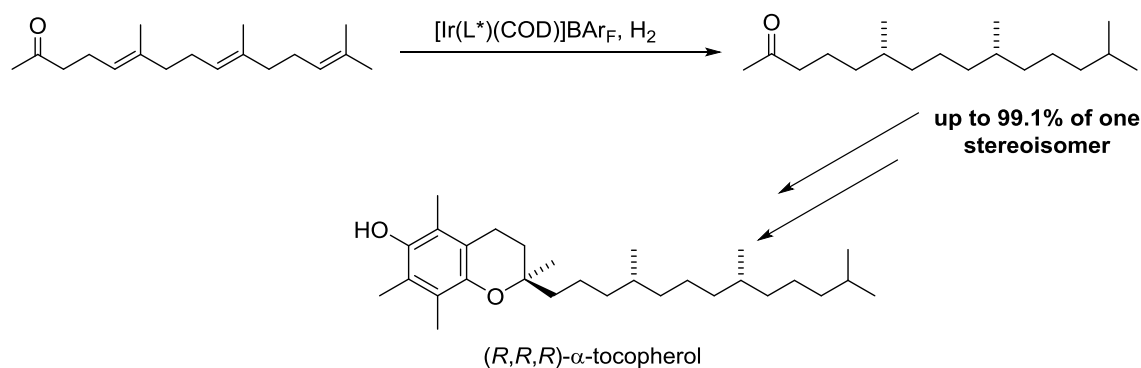
Significant improvements were achieved with  $\alpha,\beta$ -unsaturated esters which were hydrogenated with high conversion and excellent enantioselectivity (scheme 11.2).



**Scheme 11.2:**  $\alpha,\beta$ -Unsaturated esters as substrates in the hydrogenation with iridium-based catalysts.

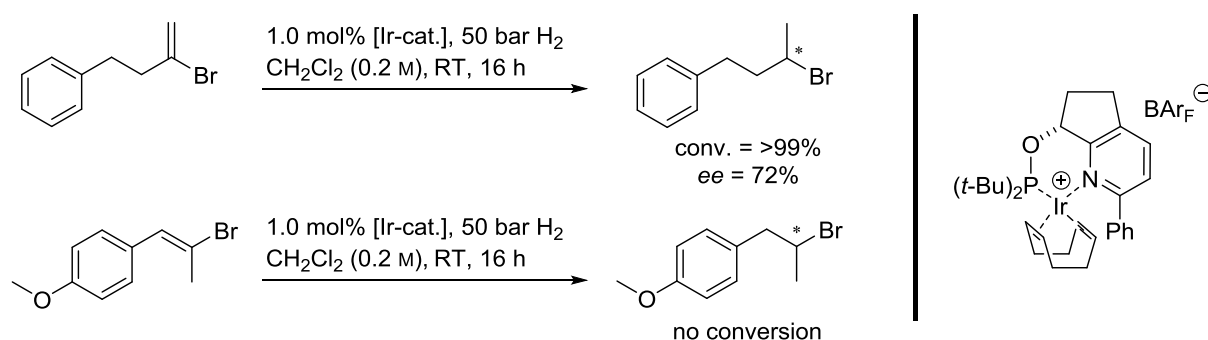


In cooperation with DSM Nutritional Products different tocopherol side chain precursors were investigated as substrates for the asymmetric hydrogenation using these new catalysts. Hydrogenations of (5*E*,9*E*)-farnesylacetone in trifluoroethanol resulted in the reduction of three C=C bonds, the introduction of two new stereogenic centers and the almost exclusive formation of the desired stereoisomers in combination with high catalyst reactivity (Scheme 11.3).



**Scheme 11.3:** Iridium N,P ligand complexes emerged as efficient catalysts for the hydrogenation of tocopherol side chain precursors.

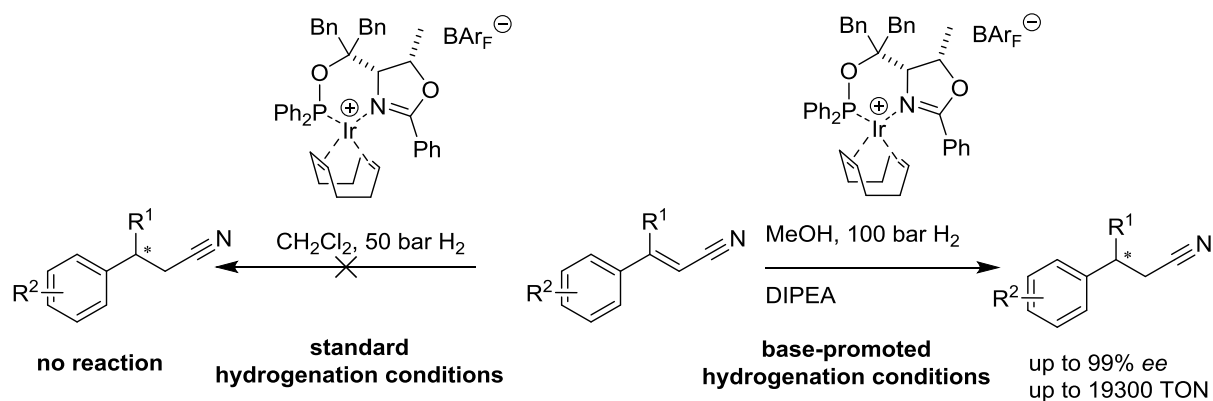
Another substrate class which was investigated in the course of this PhD thesis are vinyl bromides. Established iridium-based catalysts turned out to be extremely unreactive in the hydrogenation of this substrate class. Only terminal vinyl bromides revealed a certain reactivity. As best results, up to >99% conversion with 72% enantiomeric excess was observed (scheme 11.4).



**Scheme 11.4:** Vinyl bromides as substrates in the asymmetric hydrogenation with iridium-based catalysts.

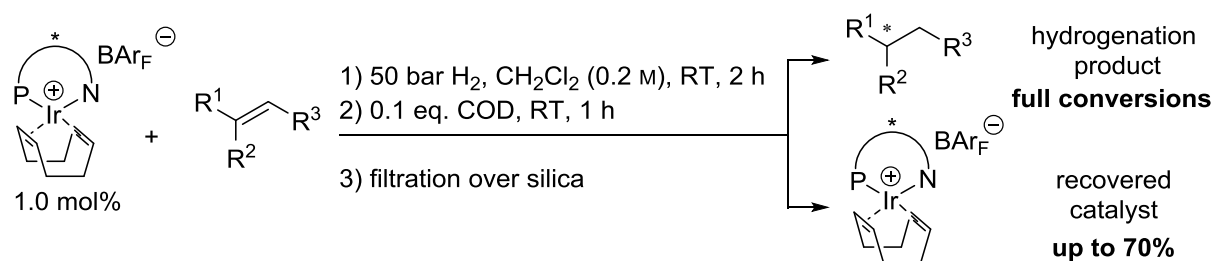
The sixth chapter of this thesis addressed the hydrogenation of  $\alpha,\beta$ -unsaturated nitriles using iridium-based catalysts. Although, first experiments revealed that iridium-based catalysts were inhibited by  $\alpha,\beta$ -unsaturated nitriles it was found that they become highly active

catalysts upon addition of *N,N*-diisopropylethylamine. The base-activated catalysts enable conjugate reduction of  $\alpha,\beta$ -unsaturated nitriles with  $H_2$  at low catalyst loadings, affording the corresponding saturated nitriles with high conversion and excellent enantioselectivity. In contrast, alkenes lacking a conjugated cyano group do not react under these conditions, making it possible to selectively reduce the conjugated  $C=C$  bond of an  $\alpha,\beta$ -unsaturated nitrile, while leaving other types of  $C=C$  bonds in the molecule intact (scheme 11.5).



**Scheme 11.5:** Base-promoted asymmetric hydrogenation of  $\alpha,\beta$ -unsaturated nitriles with iridium-based catalysts.

In the last chapter of the thesis new experimental data gained on the behavior of iridium N,P ligand complexes in the absence of substrate were used to develop an efficient protocol for the recovery of N,P ligand complexes. Upon addition of COD after the hydrogenation reaction it was possible to recover up to 70% of the catalyst. The recovered catalysts gave similar conversions and the same enantiomeric excesses as the original catalysts (scheme 11.6).



**Scheme 11.6:** Schematic diagram of the protocol applied for the recovery of the catalyst from the reaction mixture.

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Place of Birth: Bad Säckingen, Germany

Nationality: German

### **Education**

#### *University:*

- 5.2010-4.2014      Ph. D. work under the supervision of Prof. Dr. Andreas Pfaltz  
University of Basel, Switzerland
- In the field of asymmetric iridium catalyst hydrogenation
- 5.2010              M. Sc. in Chemistry, University of Basel, Switzerland
- 9.2008-5.2010      Master work under the supervision of Prof. Dr. Andreas Pfaltz  
University of Basel, Switzerland; *Synthese von sterisch anspruchsvollen  
P,N-Liganden für die iridiumkatalysierte asymmetrische Hydrierung*
- 2.2009-7.2009      Six month internship at Novartis Pharma AG Basel in the GDC/HLO  
(Hit to Lead optimization)-group under supervision of Dr. C. Markert,  
Novartis Pharma AG, Basel
- 11.2005-9.2008      B. Sc. in Chemistry, University of Basel, Switzerland

### **Awards**

- 2) 2013 SCNAT/SCS Chemistry Travel Award
- 1) SCS DSM prize for the best poster in the Organic Chemistry section (Runner's up), Fall Meeting of the Swiss Chemical Society, ETH Zürich (CH), September 2012.

### **Presentations**

#### Oral communications

- 1) *Chiral Iridium N;P Ligand Complexes and their Application in the Asymmetric Hydrogenation*, PCC Research Seminar, University of Basel (CH), Dezember 2012.
- 2) *Asymmetric Hydrogenation of  $\alpha,\beta$ -Unsaturated Nitriles Using Chiral Iridium N,P Ligand Complexes*, European symposium on organic reactivity, Prag (CZ), September 2013.

#### Poster Presentations

- 8) *Selective Asymmetric Hydrogenation of  $\alpha,\beta$ -Unsaturated Nitriles Using Chiral Iridium N,P Ligand Complexes*, Heidelberg Forum of Molecular Catalysis, Heidelberg (D), June 2013.

- 7) *Chiral Pyridyl Phosphinites with Large Aryl Substituents as Efficient Ligands for the Asymmetric Iridium-Catalyzed Hydrogenation*, Chemistry Symposium in Memory of Prof. Schönbein, Basel (CH), May 2013.
- 6) *Asymmetric Hydrogenation of  $\alpha,\beta$ -Unsaturated Esters using Iridium N,P Catalysts*, Fall Meeting of the Swiss Chemical Society, ETH Zürich (CH), September 2012.
- 5) *Asymmetric Hydrogenation of  $\alpha,\beta$ -Unsaturated Esters using Iridium N,P Catalysts*, 32<sup>th</sup> Regio Symposium of the Cross-Border University Study on Organic and Bioorganic Chemistry, Beuggen (GER), September 2012.
- 4) *Chiral Pyridyl Phosphinites with Large Aryl Substituents as Efficient Ligands for the Asymmetric Iridium-Catalyzed Hydrogenation*, Bürkenstock Conference 47<sup>th</sup> Euchem Conference on Stereochemistry, Brunnen (CH), May 2012.
- 3) *Chiral Pyridyl Phosphinites with Large Aryl Substituents as Efficient Ligands for the Asymmetric Iridium-Catalyzed Hydrogenation*, Fall Meeting of the Swiss Chemical Society, EPFL Lausanne (CH), September 2011.
- 2) *Chiral Pyridyl Phosphinites with Large Aryl Substituents as Efficient Ligands for the Asymmetric Iridium-Catalyzed Hydrogenation*, Heidelberg Forum of Molecular Catalysis, Heidelberg (GER), July 2011.
- 1) *Chiral Pyridyl Phosphinites with Large Aryl Substituents as Efficient Ligands for the Asymmetric Iridium-Catalyzed Hydrogenation*, 17<sup>th</sup> European Symposium on Organic Chemistry, Crete (GR), July 2011.

#### TEACHING EXPERIENCES AND OTHER PROFESSIONAL ACTIVITIES

- |           |   |
|-----------|---|
| 2010-2011 | Laboratory teaching assistant, Department of Chemistry, University of Basel, supervision of chemistry students in basic and advanced organic chemistry  |
| 2012      | Individual supervision of chemistry students in scientific laboratory, Department of Chemistry, University of Basel   |
| Fall 2011 | <p>Checking of a procedure to be published in <i>Organic Syntheses: Org. Synth.</i> <b>2012</b>, 89, 255-266.</p> <p>Synthesis of (<i>R</i>)-2-methoxy-<i>N</i>-(1-phenylethyl)acetamide via dynamic kinetic resolution</p> |

During my education at the University of Basel, I attended lectures given by:

W. Bonrath, E. C. Constable, B. Giese, P. C. Hauser, C. E. Housecroft, J. P. Maier, M. Mayor, W. P. Meier, M. Meuwly, A. Pfaltz, C. Schönenberger, M. Schwarz, T. Ward, H. Wegner, H. Wennemers, H.-J. Wirz.